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MANUAL OF PHYSIOLOGY

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MANUAL
OF
PHYSIOLOGY

FOR STUDENTS AND PRACTITIONERS

BY

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EXAMINER IN PHYSIOLOGY FOR THE PRIMARY FELLOWSHIP OF THE
ROYAL COLLEGE OF SURGEONS OF ENGLAND
FORMERLY LECTURER ON, AND SENIOR DEMONSTRATOR OF PHYSIOLOGY
IN KING'S COLLEGE, LONDON

WITH ONE PLATE AND 135 *FIGURES IN THE TEXT*

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PLATE I.

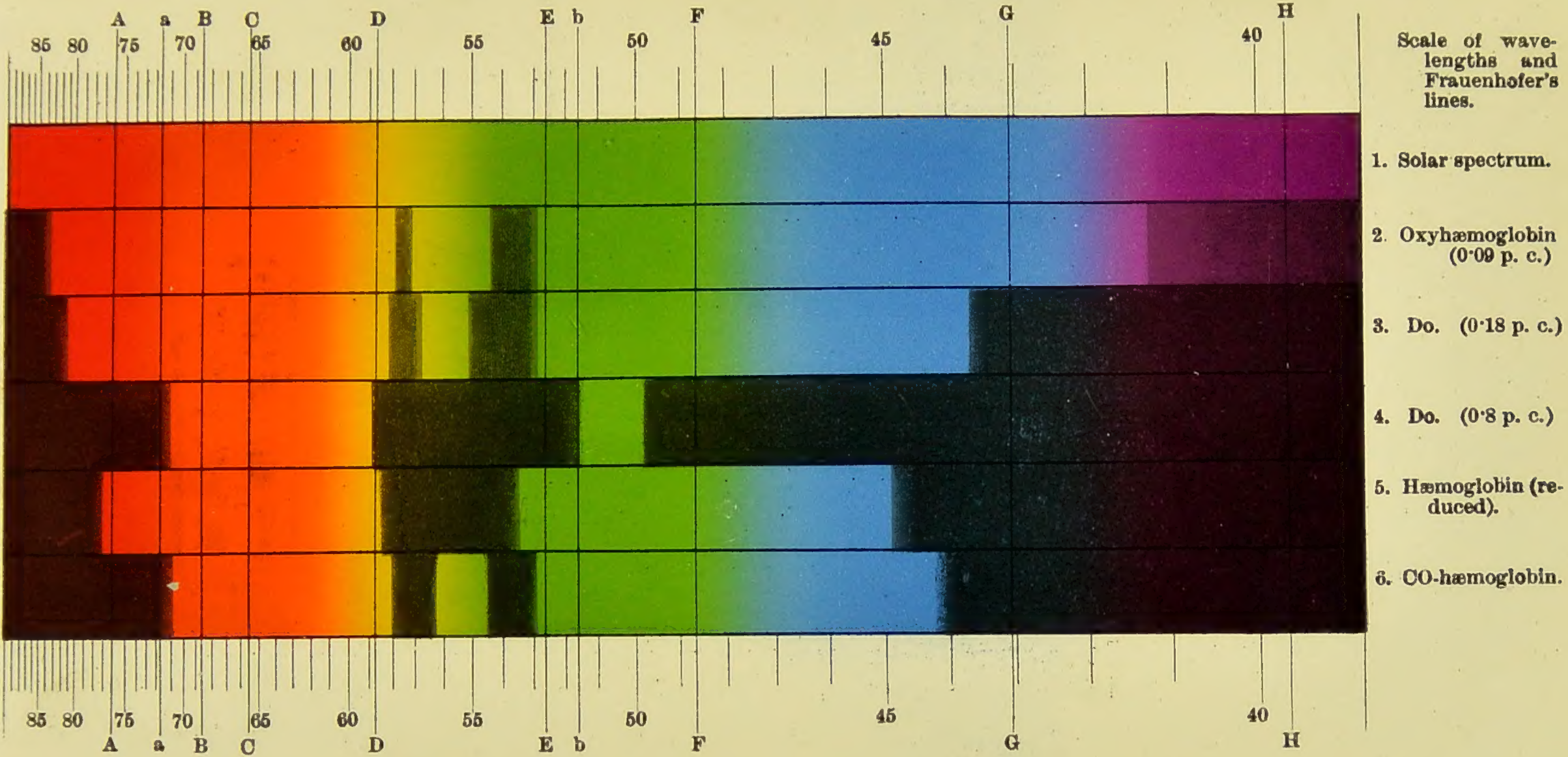
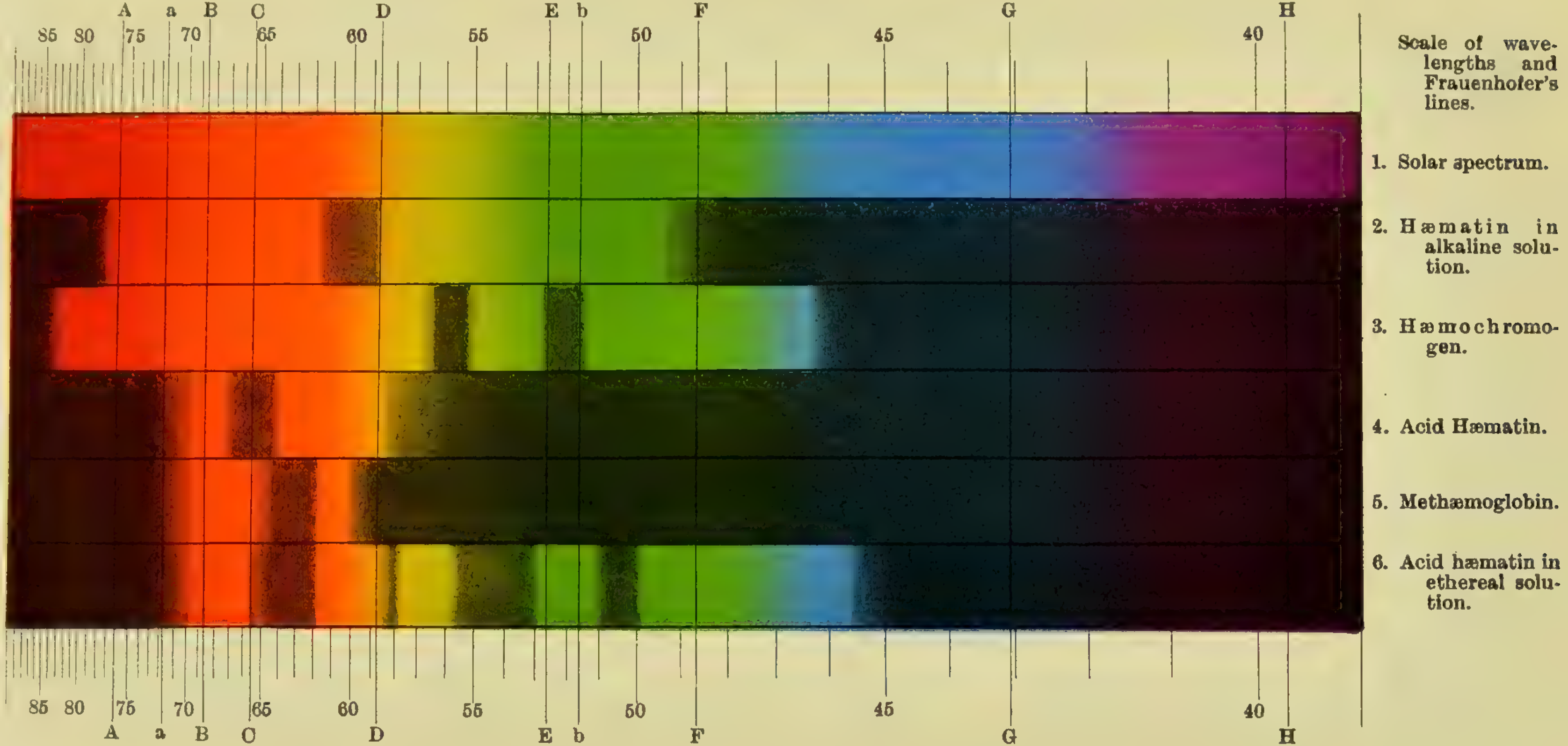

Scale of wave-lengths and Frauenhofer's lines.
1. Solar spectrum.
2. Oxyhæmoglobin (0·09 p. c.)
3. Do. (0·18 p. c.)
4. Do. (0·8 p. c.)
5. Hæmoglobin (reduced).
6. CO-hæmoglobin.
A a B C D E b F G H
85 80 75 70 65 60 55 50 45 40

PLATE II,


Scale of wave-lengths and Frauenhofer's lines.
1. Solar spectrum.
2. Hæmatin in alkaline solution.
3. Hæmochromogen.
4. Acid Hæmatin.
5. Methæmoglobin.
6. Acid hæmatin in ethereal solution.
A
a
B
C
D
E
b
F
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85
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PREFACE.

In compliance with a suggestion that the student of Physiology may have a book of convenient size, and at the same time sufficiently comprehensive, this Manual has been written. In writing it, I have endeavoured to place before the student, as concisely as possible, the chief facts of Physiology, and with this end in view, have embodied the notes of the lectures, somewhat elaborated, which during the last sixteen years I have given to the members of my classes at King's College, London.

The subject of Histology, so admirably dealt with elsewhere, has only been referred to in this volume in those cases where it directly bears upon the physiology of the organ under consideration. Similarly the Science of Embryology has not been dealt with seeing that it rather belongs to the province of Anatomy than to that of Physiology.

Diagrams of instruments and details of experiments have, so far as possible, been purposely omitted, as I am convinced that accurate knowledge of these subjects can only be properly acquired in a physiological laboratory, and this Manual is in no way intended to supply the place of a practical text-book.

In writing this book it has been my hope that it may prove of use not only to the student, but also to the practitioner, and I have endeavoured, wherever possible, to indicate the bearing of Physiology upon Practical Medicine and Surgery.

In preparing this Manual, I have had the advantage of the help and advice of my friend and former pupil, Mr. Stanley Ritson, B.Sc.(Lond.), M.R.C.S., in dealing with portions of the book, and in the reading and revision of the proof sheets. My indebtedness is also due to my friends, Mr. G. J. Jenkins, M.B., F.R.C.S., Dr. F. E. Taylor, M.Sc., M.R.C.P., F.R.C.S., and Dr. W. d'Este Emery, B.Sc.(Lond.), for their kindly help and advice in reference to those portions of the book of which the subject-matter has been their especial study. My affectionate and grateful thanks are due to my father, Mr. Thomas Lyle, M.A., for his example and sympathetic interest; he has spared no pains in correcting the proofs and preparing the index of this Manual. This index, while not absolutely exhaustive, will, it is hoped, be found to meet all the requirements of the reader.

For the preparation and arrangement of the Manual I alone am responsible, and I shall be grateful to friendly critics for any suggestions or corrections, which may be found useful in the future.

H. WILLOUGHBY LYLE.

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MANUAL OF PHYSIOLOGY.

SECTION I.

GENERAL PHYSIOLOGY.

CHAPTER I.

INTRODUCTION.

HUMAN physiology deals with the functions of the various parts of the body. The body, as a whole, is made up of different systems, such as the digestive system, the circulatory system, the respiratory system, the muscular and skeletal systems, the excretory system, and the nervous and special sense systems. Each of these has its special functions to perform, but it cannot be too strongly insisted that these systems do not act independently of each other, and that the proper working of one depends upon the harmonious working of the others.

The various systems are made up of organs which have no independent action, the smooth working of one organ depending upon the proper functioning of other organs.

The organs of the body are composed of tissues, namely—

1. Epithelial tissues.
2. Connective tissues.
3. Muscular tissues.
4. Nervous tissues.

These in their turn are essentially composed of cells, held together by a varying amount of intercellular material. Each cell consists of a mass of protoplasm or bioplasm with a nucleus embedded in the bioplasm.

The animal kingdom may be divided into two great classes, namely, the unicellular organisms, or Protozoa, and the multicellular organisms, or Metazoa. The Amœba may be taken as the simplest type of the Protozoa; it exemplifies in a simple way the chief characteristics of life, not only of the simplest, but also of the most complex, organisms.

The Amœba is a little mass of protoplasm, which readily glides along by means of protruding and retracting pseudopodia. The protrusion is due to the clear material of the cell flowing out of the more spongy network, and the retraction to its return. The cell substance on the surface is clear and firm. This is the ectosarc. That in the interior is more fluid, and contains abundant granules, of which some are protein, others fat. This is the endosarc. In the centre of the endosarc is the nucleus. The Amœba feeds by putting out pseudopodia around minute Algæ, and, in a similar manner, it engulfs drops of water. After the digestible portions of the food have been absorbed, the undigested part is excreted at any part of the protoplasm. The protoplasm contains one or more contractile vacuoles which are excretory in function, and therefore get rid of waste products. As a result of favourable nutritive conditions, the young Amœba grows and, at the limit of growth, reproduces. The usual method of such reproduction is for the nucleus and protoplasm to divide into two.

The Amœba exemplifies in a primitive way all the important characteristics of life, which may be summed up as follows :—

Movement.—This is the result of stored energy and is carried out in the higher types by means of the muscles.

Irritability.—In response to external stimuli movement is brought about. If the pseudopodia of the Amœba are stimulated by contact with a cover-glass they are withdrawn. In the higher types this irritability is associated with the nervous system.

Digestion.—Food particles are surrounded by the protoplasm of the animal, and are in all probability digested by intracellular enzymes.

Absorption.—The products of digestion are taken into the protoplasm of the cell and assimilated, or anabolised; that is, they are built into the protoplasm of the cell.

Excretion.—Waste material, such as the indigestible portions of the food and water with contained salts, is eliminated from the body.

Respiration.—All animals require oxygen, and, as the result of the oxidation, or the combustion of complex carbohydrate radicals contained in the cell body, energy results, heat is evolved, and carbon dioxide and water are produced to be eliminated from the body of the organism.

Growth.—As a result of nutrition, in favourable circumstances, growth takes place, and maturity is eventually reached, after which *Reproduction* usually occurs. All these functions of life are exhibited by the Amœba, a single cell, but physiologically complete in itself. In the multicellular organisms, masses of cells become differentiated to form organs, and hence division of labour arises. In the higher organisms, developed from a three-layered blastoderm, the cells of the outer layer become protective, muscular (muscle of the hair follicles), nervous, and sense organs. Those of the middle layer become supporting and muscular, and in general form the chief connective tissues including the circulatory and genito-urinary systems. Those of the inner layer digest and then absorb the digested food; they also give rise to the cells of the respiratory tract. It must, however, be kept in mind that each cell remains a living unit, and each has its particular function to perform. Hence the importance of dealing in detail with the structure and functions of a typical animal cell.

Some of the processes which occur in the body may be readily explained in chemical terms (chemical affinity), others are explained in physical terms (physical force). There are other processes, however, which cannot be explained by either of these methods. It is essential, therefore, to introduce a third force in explanation of these; it may be termed a biological force, and is sometimes alluded to as the biotic activity, or physiological activity, of a cell or tissue.

CHAPTER II.

THE ANIMAL CELL.

A TYPICAL animal cell consists of a mass of protoplasm, or bioplasm, with a central nucleus, near which there may be a centrosome and an attraction sphere.

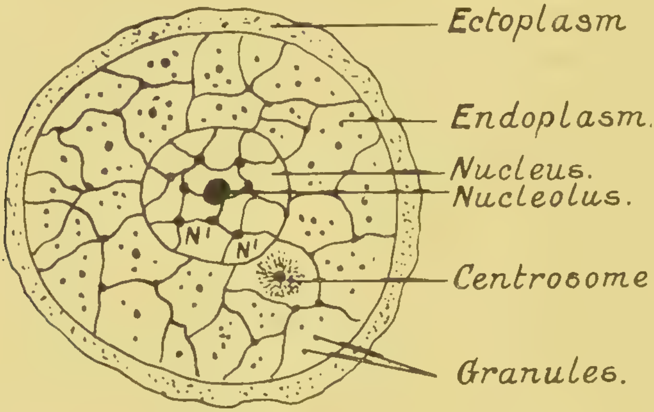


FIG. 1.—Diagram of a typical Animal Cell.

The ectoplasm may be surrounded by a cell membrane.
The endoplasm consists of a network of spongioplasm and the clearer hyaloplasm which contains granules (paraplasm).
The nucleus contains a nucleolus and many false nucleoli (N^1), which are thickenings in the intranuclear network. The nuclear sap is in the meshwork of the intranuclear network.

HISTOLOGY OF THE CELL.

The Protoplasm.—It is generally believed that the bioplasm consists of two parts, namely, a fine network called the reticulum, or spongioplasm, and a more fluid portion in its meshes, the enchylema, or hyaloplasm. The granules in the cell are due to thickenings in the spongioplasm ; some, however, are free in the hyaloplasm. Some of these granules are portions of the protoplasm, others are stored within the cell and are called cell-contents or paraplasm. The protein granules within the cell may be fixed by exposing the cells, freshly teased in aqueous humour, to the vapour of osmic acid (1 per cent. solution). Some granules stain more readily with a solution of methylene-blue (basophilous granules), others stain more readily with a weak solution of eosin (eosinophilous or oxyphilous granules).

The Nucleus.—Each cell has at least one nucleus, which is usually round, but it may be oval and is sometimes irregular. It is made up of four parts—

(*a*) A thin nuclear membrane which encloses it.
(*b*) An intranuclear network, consisting of fibrils like spongioplasm, though coarser than spongioplasm.
(*c*) Nucleoli, some of which are rounded thickenings in the intranuclear network (pseudo-nucleoli); others are rounded bodies floating in the matrix (true-nucleoli).
(*d*) Matrix, or nuclear sap, which exists in the interstices of the intranuclear network.

The nuclear membrane, intranuclear network, together with the true- and pseudo-nucleoli, consist of chromoplasm, because they readily stain with logwood (hæmatoxylin), methylene-blue, and safranin. It has been shown, however, by Balbiani that it is the minute highly refracting particles, embedded in transverse rows in the clear structureless matrix of the chromoplasmic filaments, which take up these stains.

The nuclear sap is achromatic.

The nucleus exercises a trophic function over the protoplasm of the cell and its processes, for if the nucleus is injured the cell and its processes undergo dissolution.

The Attraction Sphere.—Most cells, especially when about to divide, contain near the nucleus an attraction sphere. This consists of a small round body, the centrosome, which appears to attract protoplasmic granules to it, and which gives the whole structure a radiating appearance. The giant cells, which exist in the red bone marrow, sometimes contain more than one centrosome. The attraction sphere is all important in guiding the division of the nucleus.

CHEMISTRY OF THE CELL.

After protoplasm has been killed, it yields the following substances:—

(*a*) Water, at least three-quarters of the whole, sometimes more.

(*b*) Proteins, consisting of C.H.O.N.S.

Nucleo-protein, consisting of C.H.O.N.P.; this is the most abundant cell protein.

Nuclein, consisting of C.H.O.N.P.; this is most abundant in the nuclei.

(*c*) Lipoids, present only in small quantities; they are—

Lecithin, a phosphatide, consisting of C.H.O.N.P.

Cholesterin ($C_{27}H_{45}.OH$), a terpene.

(*d*) Inorganic salts, especially potassium phosphate, also calcium and sodium phosphate, and sodium and calcium chloride.

In the paraplasm there may be present—

Pigment granules; these are especially abundant in the pigment cells of the retina.

Fat globules, especially in the adipose tissue cells; the unsaturated neutral fat, triolein, reduces osmic acid to a lower oxide of osmium, which is black; hence neutral fat containing triolein is blackened by a weak solution of osmic acid.

Glycogen; this exists in liver cells, in colourless blood corpuscles, and in the cells of the placenta. Glycogen becomes stained a brown-red colour by a weak solution of iodine.

PHYSIOLOGY OF THE CELL.

Each living cell may be regarded as a machine, or energy transformer, through which there is constantly taking place a flow of energy. The protein, which is the most abundant chemical constituent of the bioplasm of the cell, is all important, in order that the cell may carry out its function in this way. The protein of the cell, however, depends to a very considerable extent upon the *ions* of the inorganic salts supplied by the tissue lymph for its proper working. Ringer showed that the cilia of ciliated epithelial cells continued to manifest their activity when placed in certain saline solutions. The excised frog's heart will continue to contract for a long period if placed in saline solutions of particular strength. The protein of the cell probably forms loose combinations with the ions supplied to it, or *adsorbs* the inorganic ions.

It has further been shown that the various proteins possess different *residual affinities*, or powers of adsorption of these ions, for the proteins of cells appear to combine more readily with potassium and phosphatic ions; while the proteins, which exist in the blood plasma and tissue lymph, which bathe the cells and tissues of the body, are richer in sodium and chlorine ions. It is these inorganic ions contained in the cell which regulate the osmotic pressure of the cell, and if the supply of these inorganic ions to the cell by the tissue lymph runs short, the ions gradually leave the cell. In these altered circumstances the cell is no longer capable of exercising its biotic or physiological activity, and it eventually dies. It is believed that these inorganic ions, adsorbed to the protein of the bioplasm of the living cell, influence oxidation, and, when the supply of them runs short, oxidation eventually comes to an end and dissolution results. The proteins of the cell, with their adsorbed ions of the inorganic salts, hold together other proteins, fats, carbohydrates, and oxygen, constituents which are supplied to the cell through the tissue fluid. It is by the oxidation of these carbohydrates, fats, and, to a less extent, the proteins, loosely combined with the more or less stable proteins of the cell, that new forms of energy are evolved, and, as a result of such oxidative or katabolic processes, CO_2 and water are produced, while certain nitrogenous compounds are formed as the result of the wear and tear of the cell protein. These waste products are eliminated or excreted by the cells. Since CO_2 is a waste product of the process of oxidation, it might be thought that the most advantageous condition would be for its immediate removal, but it has been shown by Waller that a small amount of CO_2 acts as a stimulant. Small amounts of CO_2 increase the excitability of muscle and nerve, while large doses diminish that excitability. Haldane has also shown that a definite small percentage of CO_2 is required for the regulation of the activity of the nerve cells constituting the respiratory centre in the medulla oblongata, and that, if this percentage is reduced by artificial ventilation, the subject passes into a condition of apnœa, or suspension of breathing, until the amount of CO_2 in the lung alveoli and in the blood returns to normal. (Normally there is between 4 and 5 per cent. of CO_2 in the air of the lung alveoli.)

It is characteristic of bioplasm that oxidation processes occur, and that, as the result, energy arises and heat is evolved; but, in order that equilibrium may be maintained, anabolism or constructive metabolism or assimilation must occur in the cell. For this purpose the cells are supplied with protein, fat, carbohydrate, oxygen, and inorganic salts.

The *Proteins* are supplied to the cell to make up for that amount which has been disintegrated during cellular activity, *i.e.*, as the result of wear and tear. These may be supplied as serum-globulin and serum-albumin, which are present in the blood plasma and tissue fluid or lymph, or possibly they are supplied as mono-amino acids; for example, amino-acetic acid or glycine or glycocoll ($CH_2.NH_2.COOH$), as diamino-acids, and also as amino-acids, which contain an aromatic radical.

The *Fats* exist in the plasma, most probably adsorbed to the soluble protein present, and thus they exist, not as fat globules, but in some soluble and invisible form, and as such are taken to the cells, where they combine in a similar invisible form with the more stable cell proteins. It has been demonstrated that the liver cells are capable of holding 5 to 10 per cent. of fat, in such a way that it is quite invisible and is part of the cell bioplasm. Bainbridge and Leathes have shown that, by interfering with the blood supply of the liver, the cells may be made to appear as if they were undergoing fatty degeneration, whereas there is in reality no actual increase of fat in the organ. In other words, the fat, so observed within the cells, has probably been deposited from the cell protein which previously adsorbed it.

Carbohydrate exists in the blood plasma as dextrose, and some of this is in all probability combined in a feeble manner (adsorbed) with the blood proteins. It has been shown that, if CO_2 is passed through blood serum, or if chloroform or ether is added to blood serum, the amount of free dextrose present becomes considerably increased; this extra amount has become dissociated from the blood proteins. The carbohydrate, which is supplied to the cells of the tissues, is probably adsorbed by the fixed cell proteins, and it may be in this way that new proteins may be synthesized by the union of protein radicals, rich in amino acids and carbohydrates; in a similar way, fats may possibly be synthesized from carbohydrates.

Oxygen is supplied to the cells through the oxy-hæmoglobin, where it is loosely chemically combined with the hæmoglobin. In the higher types the oxy-hæmoglobin is contained in the coloured blood corpuscles; in some of the lower types, such as the worms, it is dissolved in the blood plasma.

Inorganic Salts, which, as has been already stated, are so essential for the biotic or physiological activity of the cells, are supplied by way of the plasma and tissue fluid or lymph, those supplied being sodium chloride, potassium chloride, calcium salts, and phosphates, whereas those found in the cells are chiefly potassium and phosphatic ions, suggesting that the cell proteins have some selective action for particular ions. Though the inorganic ions are adsorbed to the cell proteins, yet it is quite possible that each ion is capable of exerting its own osmotic pressure.

The *Lipoids* of the cell play an important part in preserving the life of the cell, since they have the power of combining with organic poisons and toxins, which enter the body usually through the alimentary canal, or by way of the skin through the lymph stream present. In this way the bioplasm of the cell is guarded from these toxic influences, which might otherwise cause the death of the cell.

It will be shown later that some of the cells of the tissues and organs produce, and therefore contain, intracellular *enzymes*. In some instances the action of these bodies serves to explain some of the physiological processes which take place in the cells and tissues of the body (*vide* "Tissue Enzymes," p. 58).

Summing up, then, it may be said that "the living cell exists in a periodically varying osmotic equilibrium with its surroundings," that, as the result of its biotic activity, oxidative changes must occur with the production of energy, heat, and waste products (katabolism or destructive metabolism). As the result of these changes, unless death is to take place and these processes brought to an end, constructive metabolism, anabolism, or assimilation must be continually occurring. These processes, therefore, which are continually going on, constitute metabolism; when metabolism comes to an end, life ceases to exist. The metabolic changes which have been described as occurring in a typical animal cell, the physiological unit, are characteristic of those which take place in the individual, the physiological whole. As the body is composed of various organs, a division of labour is a necessary result, each organ having its own proper function to perform.

These organs are all under the influence of, and governed by, the cells contained in the nervous system, and also are influenced by various chemical excitors, internal secretions, or hormones, which are produced in particular organs of the body. In this way it is that the organs are brought under central control; and, as a consequence, under physiological conditions, act in perfect harmony and therefore for the benefit of the individual.

CELL MOVEMENT.

Cell movement is seen to occur in amœboid and other cells; this movement may be spontaneous, but it is usually influenced by external stimuli. If the cell moves towards the stimulus, the term positive taxis is applied to it; if away from the stimulus, negative taxis. Cell movement is influenced by the following circumstances:—

(*a*) *Alterations of Temperature.*—The optimum temperature for cell movement is 37° C. to 38° C. If the temperature is lowered towards freezing-point, movement is inhibited and finally stops, but reappears again on raising the temperature. If the temperature is raised to 45° C., the proteins of the cell are coagulated, heat rigor occurs, and the protoplasm is killed.

(*b*) *Light.*—The pigment cells present in the skin of the frog contract when exposed to bright light and expand when the amount of light is diminished. When light rays fall upon the retina there is a certain amount of movement in the pigment cells present. The general effect of light is to increase the physiological activity of cells.

(*c*) *Electrical Stimuli.*—Weak currents stimulate protoplasmic movement; strong currents inhibit movement.

(*d*) *Mechanical stimuli*, *e.g.* the pseudopodium of the amœba (*vide* p. 2).

The effects of various stimuli upon unicellular organisms have been investigated, and the following terms have consequently been introduced: thermo-taxis, photo-taxis, galvano-taxis, chemo-taxis, which explain themselves.

CELL-DIVISION.

Cells multiply by simple division, or by dividing into two, but the division of the bioplasm is preceded by the division of the nucleus.

There are two forms of nuclear division, namely—

1. Direct, simple, akinetic (α, no, κίνησις, movement), or amitotic division, in which the nucleus constricts at its centre, and divides into two equal parts; this change is often preceded by division of the true nucleolus.
2. Indirect division, or karyokinesis (κάρυον, a kernel), or mitosis (μίτος, a thread), this being the usual method.

The stages in karyokinetic division are as follows:—

(*a*) *The Reticulum.*—This constitutes the resting condition of the mother nucleus. The centrosome splits into two and the two halves separate, attracting the cell granules and constituting the attraction spheres.

(*b*) *The Spirem.*—The intranuclear network becomes arranged in the form of a spiral thread, which is at first open, later closed. This thread splits into V-shaped loops or chromosomes. In cells, which divide as the result of fertilisation, the number of chromosomes is even, an equal number being contributed by each sex; in the human fertilised cell there are sixteen chromosomes. The nucleoli disappear and the nuclear membrane becomes less distinct, so that the hyaloplasm of the cell and the nuclear sap become intermingled. An achromatic spindle appears, formed of thin achromatic fibres, which connect one daughter centrosome to the other. Around the spindle the chromosome threads are irregularly arranged. The achromatic spindle is probably formed from the two centrosomes and the achromatic substances in the nucleus.

(*c*) *Cleavage.*—Each chromosome moves towards the centre of the achromatic spindle, and splits longitudinally into two daughter threads.

(*d*) *Monaster or Star.*—The achromatic spindle becomes longitudinal and the split chromosomes arrange themselves in a star-shaped manner around the equator of the spindles.

(*e*) *Metakinesis or Divergence.*—The polar bodies or centrosomes at the ends of the spindle appear to attract the daughter V's which move along the fibres of the spindle. It may be that the V's are pulled into their new position by the contraction of the fibres of the spindle to which they are attached.

(*f*) *Diaster or double Star.*—The V-shaped filaments are conveyed to the centrosomes of the spindles and the fibres of the spindle split at the equator. The bioplasm of the cell now commences to split.

(*g*) *Dispirem or double Skein.*—An open skein is formed in the daughter nuclei, later the chromosomes unite to form a closed skein in each daughter nucleus.

(*h*) *Reticulum.*—The resting stage of each daughter nucleus; the bioplasm of the original cell having split at the same time as the nucleus divided, two resting cells are consequently produced. A nuclear membrane forms around each daughter nucleus, and the remains of the spindle gradually disappear.

The time occupied by karyokinesis varies from a half an hour to three hours.

Many of the changes described may be seen in the cells of the epidermis contained in a section of a newt's tail.

SECTION II.

CHEMICAL PHYSIOLOGY.

CHAPTER III.

THE PROTEINS.

PROTEINS are complex substances which belong to the class of bodies designated by Graham as "Colloids." They are made up of carbon, hydrogen, oxygen, nitrogen, and, in nearly all cases, sulphur. Some of the proteins also contain phosphorus and iron; other elements, such as iodine (in iodothyrin of the thyroid gland), may also be present.

The proportion of these elements varies considerably in the different proteins, but the general percentage composition is as follows:—

C	53 per cent.
H	7 ,,
O	22 ,,
N	16 ,,
S	1 to 2 ,,

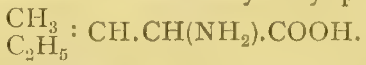
The term protein is used, however, to designate that group of substances, which consist of combinations of amino-acids, *e.g.* amino-acetic acid or glycocoll, amino-propionic acid or alanine, phenyl-amino-propionic acid or phenyl-alanine, guanidine-amino-valeric acid or arginine, etc. The proteins, therefore, are substances of large molecular weight, which essentially consist of groups of amino-acids forming polypeptides. During the digestion of the proteins of the food, they are, by a process of hydrolysis, broken into simple substances of lighter molecular weight, called cleavage products, and these are chiefly amino-acids. It is these which are so important to the body for the constructive metabolism or anabolism of its native proteins, such as serum-globulin, serum-albumin of the blood and tissue fluids (lymph, cerebro-spinal fluid, aqueous humour), and the nucleo-proteins, globulins, and albumins of the cells and tissues of the body. The proteins are essentially polypeptides formed by the condensation of varying numbers of groups of amino acids which may be obtained from the proteins by hydrolysis. In nearly all instances ammonia may also be obtained on hydrolysis. The nitrogen of the mono-amino acids is called "mono-amino-nitrogen," that of the diamino acids is called "diamino or basic nitrogen," and the nitrogen, obtained by the hydrolysis of proteins in the form of ammonia, is called "amide-nitrogen."

The following are some of the cleavage products of **Proteins** due to hydrolysis :—

1. MONO-AMINO ACIDS.

One COOH Group, *i.e.* Mono-carboxylic Group.

Glycine = Amino-acetic acid = $CH_2.NH_2.COOH$.
Alanine = Amino-propionic acid = $C_2H_4.NH_2.COOH$.
Valine = Amino-isovaleric acid = $C_4H_8NH_2.COOH$.
Leucine = Amino-isocaproic acid = $C_5H_{10}.NH_2.COOH$.
Isoleucine = Amino-methyl-ethyl-propionic acid =



$$\begin{matrix}CH_3\\C_2H_5\end{matrix} : CH.CH(NH_2).COOH.$$

Serine = Hydroxy-amino-propionic acid = $CH_2(OH).CH.NH_2.COOH$.
Cystine or dicysteine = Di-(thio-amino-propionic acid) = $C_6H_{12}N_2O_4S_2$.

Two COOH Groups, *i.e.* Dicarboxylic Group.

Aspartic acid = Amino-succinic acid = $COOH.CH_2.CH(NH_2).COOH$.
Glutamic acid = Amino-glutaric acid = $COOH.CH_2.CH_2.CH(NH_2).COOH$.

Aromatic Amino-acids or Ringed Groups.

Phenylalanine = Phenyl-amino-propionic acid = $C_6H_5.C_2H_3.NH_2.COOH$.
Tyrosine = Hydroxy-phenyl-amino-propionic acid = $(C_6H_4.OH).C_2H_3.NH_2.COOH$.
Tryptophane = Indole-amino-propionic acid = $C_{11}H_{12}N_2O_2$.

2. DI-AMINO ACIDS.

Ornithine = Diamino-valeric acid = $C_4H_7.(NH_2)_2.COOH$.
Lysine = Diamino-caproic acid = $C_5H_9.(NH_2)_2.COOH$.
Arginine = Guanidine-amino-valeric acid = $C_6H_{14}N_4O_2$.

Lysine ($C_6H_{14}N_2O_2$), Arginine ($C_6H_{14}N_4O_2$), Histidine ($C_6H_9H_3O_2$), although under the heading acids, may also play the part of bases, and as each contains Carbon six times, they are frequently known as the hexone bases.

3. PYRROLIDINE DERIVATIVES.

Proline = Pyrrolidine carboxylic acid = $C_5H_9NO_2$.
Oxy-proline = Oxy-pyrrolidine carboxylic acid = $C_5H_7NO_3$.
The N is included in the benzine ring formation.

4. AN IMIDAZOLE RING.

Histidine = Imidazole-amino-propionic acid = $C_6H_9N_3O_2$.

5. PYRIMIDINE BASES.

These are cleavage products of nucleo-proteins—
Uracil = Dioxy-pyrimidine.
Thymine = Methyl-dioxy-pyrimidine.
Cytosine = Amino-oxy-pyrimidine.

6. PURINE BASES.

These are cleavage products of nucleo-proteins—
Adenine or amino-purine ($C_5H_3N_4.NH_2$).
Guanine or amino-oxypurine ($C_5H_3N_4O.NH_2$).

7. AMMONIA.

It will be remembered that these substances just described, and many others, are the units or "foundation stones" of which the protein molecule is built, hence its complexity. The complex protein molecule may be broken into the parts of which it is composed by hydrolysis. This may be effected by the action of acids (dilute sulphuric acid, hydrochloric acid), by the action of alkalies (baryta water) and the various proteoclastic enzymes which occur in plants and in animals.

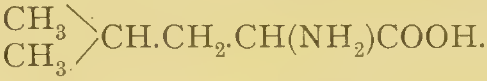
The result of hydrolysis shows that the various proteins are composed of the same units or "foundation stones"; in some cases, however, certain units are missing, in others one or other unit may be present in large amount.

Glycine, glycocoll, or amino-acetic acid ($CH_2.NH_2.COOH$), is the simplest of the products of the hydrolysis of proteins. It is not present in albumin, caseinogen, or in hæmoglobin. It is present only in small quantities in the vegetable proteins. Glycocholic acid of bile may be split into glycine and cholalic acid. Hippuric acid of urine may be split into glycine and benzoic acid.

Alanine, or amino-propionic acid ($C_2H_4.NH_2.COOH$), is a constant constituent of all proteins. The following are some of the derivatives of alanine: serine, phenyl-alanine, tyrosine, tryptophane, and histidine.

Valine, or amino-isovaleric acid ($C_4H_8.NH_2.COOH$), has been obtained from the protamine, clupeine, also from caseinogen and from horn.

Leucine, or amino-isocaproic acid ($C_5H_{10}.NH_2.COOH$), is, with the exception of arginine, the most widespread of all the amino-acids which go to make up the protein molecule (Aders Plimmer). Leucine is α-amino-iso-butyl acetic acid—



$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>CH.CH_2.CH(NH_2)COOH.$$

Isoleucine, or α-amino-β-methyl-β-ethyl-propionic acid, is present in fibrin. It is a widely distributed constituent of the protein molecule. Both leucine and isoleucine occur in the protein molecule combined with tyrosine and valine in the form of polypeptides.

Phenyl-alanine, or phenyl-amino-propionic acid ($C_6H_5.C_2H_3.NH_2.COOH$), is in some proteins present in excess of tyrosine, and is the principal aromatic constituent. Gelatine contains no tyrosine, but phenyl-alanine is present.

Tyrosine, or oxy-phenyl-amino-propionic acid ($C_6H_4.OH.C_2H_3.NH_2.COOH$), is present in most proteins, and is readily obtained by the action of the enzyme trypsin upon protein.

Cystine, or dicysteine, has the following composition:—

$$COOH.CH(NH_2).CH_2—S—S—CH_2.CH(NH_2).COOH.$$

It is the only sulphur-containing compound in the protein molecule. The taurine of the bile is probably derived from it. The cystine of protein and the cystine of urinary calculi appear to be identical; hence it is probable that the cystine, which is present in some urinary calculi, is derived from cystine present in protein.

Aspartic acid, or amino-succinic acid ($COOH.CH_2.CH(NH)_2.COOH$), may be obtained from certain vegetable proteins as a result of tryptic digestion. Asparagine, the amide of aspartic acid ($CONH_2.CH_2.CH(NH_2).COOH$), is present in the proteins of asparagus and the seeds of peas; it is probably derived from the aspartic acid contained in the protein of the seeds.

Glutamic acid, or amino-glutaric acid ($COOH.CH_2.CH_2.CH(NH_2)COOH$), was first obtained from wheat glutin by hydrolysis. It has been since obtained by the action of the enzyme trypsin upon fibrin.

Ornithine, or diamino-valeric acid ($NH_2.CH_2.CH_2.CH_2.CH.NH_2.COOH$), on hydrolysis gives rise to CO_2 and putrescine or tetramethylene-diamine.

Arginine, or guanidine-amino-valeric acid ($C_6H_{14}N_4O_2$), has been obtained from the products of hydrolysis of horn, gelatin, vitellin, egg-albumin, serum-albumin, and caseinogen. It occurs in the protamines and histone. Arginine may be hydrolysed by the enzyme arginase into ornithine and urea.

Lysine, or diamino-caproic acid ($C_5H_9(NH_2)_2.COOH$), is present in caseinogen, gelatin, egg-albumin, fibrin, and in the protamines.

Histidine, or imidazole-amino-propionic acid ($(C_3H_3N_2)C_2H_3(NH_2).COOH$), was discovered by Kossel amongst the decomposition products of sturine, the protamine obtained from the testes of the sturgeon. It has also been obtained by the action of the enzyme trypsin upon fibrin.

Tryptophane, or indol-amino-propionic acid, was isolated by Hopkins and Cole from the products found by the action of trypsin upon caseinogen.

Tryptophane in the protein molecule accounts for the three following phenomena :—

1. If Cl or Br water is added to a tryptic digest, a reddish-violet colour is produced.
2. The violet colour obtained in the Adamkiewicz reaction.
3. The presence of indole and skatole as products of putrefaction, for when tryptophane is heated, large amounts of indole and skatole are produced.

CLASSIFICATION OF PROTEINS.

The **Proteins** may conveniently be divided into four chief groups—

1. The Simple Proteins.
2. The Conjugated Proteins.
3. The Phospho-Proteins.
4. The Derived Proteins.

A. Simple Proteins.

1. **Protamines**. —These are the simplest of the natural proteins, and are obtained from the testes of fish ; salmine from the salmon, sturine from the sturgeon, scombine from

the mackerel, cyclopterine from the cyclopterus, clupine from the herring. The protamines are soluble in water, and are not coagulated by heat. On hydrolysis they yield protones, bodies analogous to peptones; they are readily converted into the hexone bases, namely, lysine, $C_6H_{14}N_2O_2$, or diamino-caproic acid, arginine, $C_6H_{14}N_4O_2$, or amino-guanidine-valeric acid, and histidine, $C_6H_9N_3O_2$, or imidazole-amino-propionic acid. On hydrolysis cyclopterine also yields tyrosine (oxy-phenyl-amino-propionic acid). It will be seen that the protamines are built up almost exclusively of amino-acids. It will be noted that each of these compounds has a carbon atom six times, hence the term hexone base. The protamines give Rose's, or Piotrowski's reaction. Protamines react as strong bases, and give rise to alkaline solutions and form salts with acids. The protamines do not give Millon's test except cyclopterine, the molecule of which contains tyrosine.

2. **Histones.**—These substances may be extracted from cells by the addition of an acid; the histone is then precipitated from this acid extract by the addition of ammonia, a characteristic property of histones. Kossel first isolated histone from the red blood corpuscles of the goose. *Globin*, the protein radical of hæmoglobin, is said to be a histone, the chief amino-acid present being histidine. Histones are coagulated by heat, and, on hydrolysis, yield a larger number of amino-acids than the protamines do, hence they are more complex substances. Histones contain about 30 per cent. of lysine, arginine, and histidine together.

3. **Albumins.**—The more important of the albumins are serum-albumin, lact-albumin, and egg-albumin. They form colloidal solutions in water, in dilute salt solution, and in a saturated solution of sodium chloride and of magnesium sulphate. They are readily coagulated by heat at about 70°–73° C. On hydrolysis they yield *no* glycine (amino-acetic acid). The albumins may be precipitated from their solution by complete saturation with ammonium sulphate crystals.

4. **Globulins.** — These include serum-globulin and egg-globulin. They are insoluble in distilled water, but are soluble in dilute saline solutions. They are precipitated from their solutions by complete saturation with neutral salts, such as $MgSO_4$, Na_2SO_4, or half-saturation with $(NH_4)_2SO_4$.

Amongst other substances the globulins on hydrolysis yield glycine. This class also includes fibrinogen which, on coagulation, yields fibrin, also paramyosinogen and myosinogen, the proteins of muscle, which, when coagulation occurs, yield myosin, and crystallin, the globulin which is obtained from the crystalline lens. Fibrinogen and myosinogen coagulate at 56° C., serum-globulin at about 75° C.

5. **Sclero-Proteins.**—These proteins are for the most part found in the skeletal and supporting tissues of the body, and are of an insoluble nature. The chief proteins under this heading are as follows:—

COLLAGEN.—This is contained in white fibrous tissue, and, when boiled with water, is converted into gelatin.

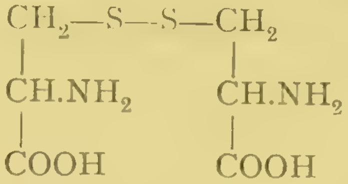
Collagen is readily digested in the stomach by the action of the pepsin-hydrochloric acid, but, in the duodenum, the trypsin-sodium-carbonate of the pancreatic juice has no appreciable digestive action upon it.

GELATIN is obtained from white fibrous tissue by boiling it in water. It is soluble in hot water, but sets in cold. It contains 17 per cent. of glycine (amino-acetic acid), and a considerable amount of proline, but *no* tyrosine, tryptophane, or cystine is in its molecule. It will not, therefore, give Millon's test for protein, nor will it give the xanthoproteic reaction nor Adamkiewicz's test for protein. When in solution, gelatin readily gives Rose's test. Gelatin is, like carbohydrate and fat, a "protein-sparing food." How the gelatin spares the protein is unknown, but one view is that the gelatin shields the amino-acids, which have been taken to the liver, and prevents them from undergoing "denitrification" by the liver cells, and so allows more of the amino acids to get to the tissues, and to be utilised there for tissue repair, replacing the molecules of the tissues which have undergone wear and tear during those katabolic processes, which are constantly going on there. Gelatin will not replace simple protein of the food, for the ringed amino-acids, necessary for tissue repair, are absent from it.

ELASTIN is an almost insoluble body, which may be extracted from yellow elastic tissue by prolonged boiling; it is also contained in the sarcolemma of muscle fibres. It gives the xanthoproteic and Millon's reactions for protein. Elastin appears to be made up of only three or four amino-acids.

CHONDRIN exists in cartilage, and is said to be a compound of gelatin and mucoid. It may be obtained from cartilage by boiling.

Keratin is produced in the cells of the epidermis from the eleidin granules of the stratum granulosum. It is found in the nails, hoofs, and horns. It contains 5 per cent. of sulphur, which is present in the sulphur-containing amino-acid, cystine, which has the following formula:—



$$\begin{array}{ll} CH_2\text{—}S\text{—}S\text{—} & CH_2 \\ \vert & \vert \\ CH.NH_2 & CH.NH_2 \\ \vert & \vert \\ COOH & COOH \end{array}$$

Keratin contains more cystine than any other protein. Tyrosine is also present.

Neurokeratin is contained in the fine network in the medullary sheath of the medullated nerve fibres in both the central and the peripheral nervous system. In this connection, it should be noted that both the epidermis and the nervous system are developed from the epiblast.

Keratin and neurokeratin both give the xanthoproteic and Millon's reactions for protein.

Ossein is the chief protein contained in bone.

Chitin is the protein which is present in the exoskeleton of many of the lower types. Lobster shell consists of calcium carbonate and chitin. On hydrolysis chitin yields acetic acid and glucosamine. Chitin is said to be monoacetyl-diglucosamine (Offer).

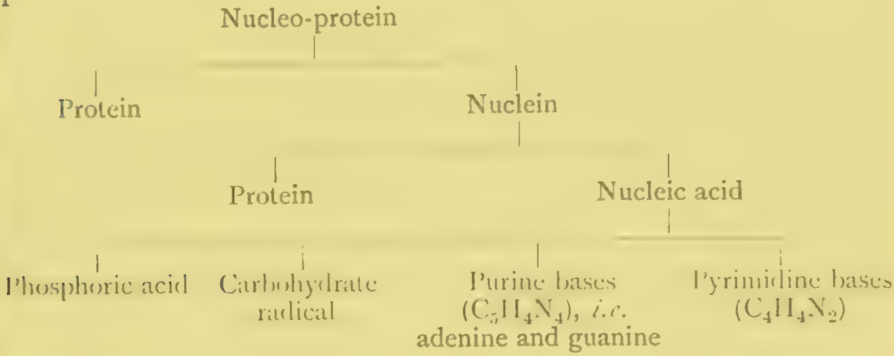
B. Conjugated Proteins.

"Proteins sometimes occur in nature combined with organic complexes, which have been designated by Hoppe-Seyler as 'prosthetic' groups, from which, by gentle chemical treatment (*e.g.* by weak acids at the ordinary temperature), they can be readily freed. These conjugated proteins give the same general chemical reactions as the simple proteins" (Schryver).

1. **Nucleo-Protein.**—This is a compound of protein with nucleic acid, and exists in the cells of the body generally. The phosphorus present is contained in the prosthetic group, nucleic acid. The hæmatogens described by Bunge, which are contained in the yolk of eggs and vegetables, and which are the chief source of iron for the body, are nucleo-proteins.

Nucleo-proteins may be prepared from tissues rich in cells, such as the kidney or thymus, by the following method :—

The organ is finely minced and then ground in a mortar with an equal volume of crystals of sodium chloride with a little water. The sticky mass is then poured into a tall vessel containing water. The nucleo-protein gradually rises to the top of the water, and may be collected as a scum. It is readily soluble in sodium carbonate, 1 per cent. solution. The following table represents the decomposition of nucleo-protein :—


Nucleo-protein
Protein
Nuclein
Protein
Nucleic acid
Phosphoric acid
Carbohydrate radical
Purine bases ($C_5H_4N_4$), *i.e.* adenine and guanine
Pyrimidine bases ($C_4H_4N_2$)

THE PURINE BASES—

Purine Bases.	$C_5H_4N_4$ . . .	Purine.
	$C_5H_3N_4.NH_2$ . . .	Amino-purine or adenine.
	$C_5H_4N_4O$ . . .	Monoxy-purine or hypoxanthine.
	$C_5H_3N_4.NH_2.O$ . .	Amino-oxy-purine or guanine.
	$C_5H_4N_4.O_2$ . . .	Dioxy-purine or xanthine.
	$C_5H_4N_4O_3$ . . .	Trioxy-purine or uric acid.

THE PYRIMIDINE BASES—

$C_4H_4N_2$ Pyrimidine.
Uracil = Dioxy-pyrimidine.
Cytosine = Amino-oxy-pyrimidine.
Thymine = Methyl-dioxy-pyrimidine.

Halliburton states that recent research indicates that there appear to be two groups of nucleic acids—

(1) NUCLEIC-ACID PROPER, which yields on decomposition :

(*a*) Phosphoric acid.
(*b*) A carbohydrate of the hexose group.
(*c*) Two purine bases : adenine and guanine.
(*d*) Two pyrimidine bases : cytosine and thymine.

(2) GUANYLIC ACID.—This is found mixed with nucleic acid. On decomposition it yields—

(*a*) Phosphoric acid.
(*b*) A carbohydrate of the pentose group.
(*c*) Guanine only.

2. **Gluco-Proteins.** — These for the most part are sticky substances, examples of which, mucin and the mucoids, obtained from the ground substance of connective tissues, may be mentioned. These gluco-proteins consist of protein with a carbohydrate radical which is glucosamine, that is, a glucose, $C_6H_{12}O_6$, in which one (OH) group is replaced by NH_2, hence the composition $C_6H_{11}O_5.NH_2$. It is true that most proteins contain a carbohydrate radical, but this is probably not glucosamine, but a carbohydrate much more intimately connected with the protein molecule than is the glucosamine with the protein in the composition of gluco-proteins. If gluco-protein, *e.g.* mucin, is heated with a little dilute mineral acid, such as H_2SO_4, a reducing but non-fermentable sugar may be freed from the original protein.

3. **Chromo-Proteins.**—This class includes oxyhæmoglobin and some of its derivatives. Oxyhæmoglobin, or, as it is sometimes called, respiratory pigment, consists of protein (histone) combined with hæmatin. The elements present in hæmoglobin are C.H.O.N.S.Fe. The iron is in combination in the hæmatin portion of the oxyhæmoglobin. Oxyhæmoglobin and its derivatives are dextro-rotatory.

C. Phospho-Proteins.

Phospho-Proteins.—These are possibly esters of phosphoric acid with proteins. The phosphorus is contained in the protein itself. This class includes *vitellin*, one of the proteins present in eggs; *caseinogen* (0·847 per cent. of phosphorus), the most abundant protein of milk; and *casein*, the protein of coagulated milk, and consequently the chief protein of cheese. On decomposition, these substances liberate phosphoric acid, but they give rise to *no* purine and *no* pyrimidine bases, and this is one important particular in which they differ from the nucleo-proteins. It should be noted that caseinogen and casein contain no carbohydrate radical. Caseinogen reacts as an acid, and, when treated with bases, it gives rise to salts, *e.g.* calcium caseinogenate present in milk. Phospho-proteins are readily decomposed by 1 per cent. caustic soda, and are thus readily distinguished from the nucleo-proteins.

D. Derived Proteins.

These substances are the products of proteolysis, or protein hydrolysis, and are formed in the intestine during the digestion of proteins.

1. **Infra- or Meta-Proteins.**—These include acid-meta-protein which is produced in the stomach during peptic digestion by the action of pepsin-hydrochloric acid upon albumin and globulin and alkali-meta-protein, which is produced during tryptic digestion by the action of trypsin-sodium-carbonate upon albumin and globulin. These bodies (acid-meta-protein and alkali-meta-protein) are soluble in weak acid and weak alkali, but are precipitated in neutral solutions. They are also precipitated like the globulins by saturation with $MgSO_4$ crystals, Na_2SO_4 crystals, or by half-saturation with $(NH_4)_2SO_4$. They differ from the globulins, however, in that they are not coagulated by heat when in solution.

2. **Proteoses.**—These include the albumoses derived from albumin, the globuloses derived from globulin, and the gelatoses derived from gelatin. They are formed during gastric and pancreatic digestion. Those which are formed during gastric digestion are the primary albumoses, and are proto-albumose and hetero-albumose, and the secondary albumose, deutero-albumose. During pancreatic digestion the albumose found is chiefly deutero-albumose. Proto-albumose is soluble in water; hetero-albumose requires a small amount of salt to hold it in solution. If, therefore, the primary albumoses are present together in solution, that solution must of necessity contain salt, and these primary albumoses may be readily separated by dialysis. As the salt dialyses out from the dialyser into the water outside, the hetero-albumose becomes precipitated. The primary albumoses (proto- and hetero-) may be precipitated like the globulins, by full saturation with $MgSO_4$, Na_2SO_4, or half-saturation with $(NH_4)_2SO_4$. They may also be precipitated by a few drops of a solution of ferrocyanide of potassium and 25 per cent. acetic acid. Deutero-albumose is soluble in water and requires full saturation with $(NH_4)_2SO_4$ to precipitate

it. It is not precipitated by a solution of ferrocyanide of potassium and acetic acid like the primary albumoses. The proteoses are not coagulated by heat.

3. **Peptones.**—These are smaller moleculed substances than the proteoses, and are produced during peptic and tryptic digestion. They give the biuret reaction, but cannot be salted out from their solution, *e.g.*, they are not precipitated by saturation with $(NH_4)_2SO_4$. They are soluble in water and are not coagulated by heat. Peptone may be precipitated by phospho-tungstic acid and by phospho-molybdic acid, also by alcohol and by tannic acid. Peptones are not precipitated by picric acid, or by trichloracetic acid, or by potassio-mercuric iodide.

4. **Polypeptides.**—These are cleavage products of protein beyond the stage of peptone. They consist of linkages of two or more amino-acids. The shorter polypeptides do not give the biuret reaction, whereas the more complex polypeptides give it readily. In this class may be included the synthetic products of Emil Fischer, which he has obtained by the synthesis of certain amino-acids.

Pepsin does not hydrolyse the polypeptides, but it hydrolyses proteins, producing proteoses and peptones. Trypsin hydrolyses most of the polypeptides, and it hydrolyses proteins, producing amino-acids and a complex polypeptide, which contains all the proline and phenylalanine which are present in the protein molecules. Intracellular enzymes are capable of hydrolysing polypeptides, which are not hydrolysed by trypsin.

Vegetable Proteins.

Vegetable proteins are divided into four groups: Phyto-albumins, Phyto-globulins, Gliadins, and Glutelins.

1. **Phyto-Albumins.**—These are the leucosins of wheat, rye, barley, and maize. They contain C.H.O.N.S., generally the N present is about 16 per cent., and the S about 1·5 per cent. They contain no phosphorus. The leucosins are coagulated at 52° C., and they give the typical protein colour reactions.

2. **Phyto-Globulins.**—These include the edestin of hemp, and legumin of peas. They contain C.H.O.N.S. There is no phosphorus present. They can be readily crystallised.

3. **Gliadins.**—These proteins are soluble in alcohol, hence

they are sometimes called the "alcohol soluble proteins." They include wheat gliadin, rye gliadin, hordein of barley, and zein of maize. Amongst their cleavage products there is a quantity of NH_3, and as much as 36 per cent. of glutamic acid. There is, however, no glycine nor lysine in their cleavage products. Rice contains no "alcohol soluble protein," whereas the gluten of wheat flour contains both gliadin and glutelin. The stickiness of dough is due to the gliadin present. Hordein contains as much as 14 per cent. of proline. Zein contains no tryptophane molecule.

4. **Glutelins.**—These vegetable proteins are insoluble in water and also in alcohol, hence are sometimes known as "alcohol insoluble proteins." They are soluble in dilute alkalies —0·2 per cent.—and are precipitated from the alkaline solutions by neutralisation with an acid. Glutelin is present, oftentimes as much as 50 per cent.; it contains phosphorus. The cleavage products of the glutelins contain 2 per cent. of lysine and 9 per cent. glutamic acid.

THE MORE IMPORTANT TESTS FOR PROTEINS.

1. The majority of proteins are coagulated by *heat.* If the solution, which contains the protein, is rendered faintly acid by the addition of two or three drops of 2 per cent. acetic acid, and then boiled, the soluble protein is coagulated.

2. *Heller's Test.*—If a solution of protein is poured on to a little concentrated nitric acid in a test-tube, a white ring forms at the junction of the protein solution with the nitric acid.

3. *The Xanthoproteic Reaction.*—If a few drops of concentrated nitric acid are added to a solution of protein, a white precipitate is produced; if this is heated, the precipitate becomes canary yellow. The mixture should then be cooled, and a few drops of ammonia solution added; the yellow colour becomes changed to orange. This reaction probably depends upon the presence of a radical containing the benzene ring.

4. *Millon's Reagent* consists of a mixture of the two nitrates of mercury containing an excess of nitric acid. If a drop of this solution is added to a solution of protein, the protein is precipitated with the mercury (mercury albuminate). If the white precipitate is heated, it coagulates, and the coagulum turns brick red. This is due to the presence of an aromatic radical (C_6H_5) in the original protein molecule. If the protein

is simply suspended in water, the xanthoproteic and Millon's tests may be obtained in the suspended solid.

5. *Rose's or Piotrowski's Test.*—If to a solution of protein just a trace of a 1 per cent. solution of copper sulphate is added, a bluish precipitate is obtained, for the protein is thrown down with the heavy metal (copper albuminate). To this a few drops of a 20 per cent. solution of caustic potash should be added; the bluish precipitate at once dissolves, and a violet colour is obtained. The colour is probably due to CO—NH complexes (Schiff), which are present in the protein molecule.

6. *Rosenheim's Formaldehyde Reaction.*—To a solution of protein, a few drops of a dilute solution of formaldehyde (1 in 2500) should be added. This mixture is then gently poured on to the top of concentrated sulphuric acid; where the two come into contact a purple ring is produced. This reaction is due to tryptophane (indole-amino-propionic acid) in the protein molecule. This reaction is not given by gelatin, which does not yield tryptophane as a product of hydrolysis.

7. If to a solution of protein a few drops of 20 per cent. acetic acid are added, and then an excess of a solution of potassium ferrocyanide, a yellowish-white precipitate is produced.

8. Some proteins, such as the gluco-proteins, give a reaction which indicates the presence of sugar, thus—

Molisch's Reaction.—To the protein solution add a few drops of an alcoholic solution of α-naphthol, then add concentrated H_2SO_4. A violet colour is produced, which turns yellow on the addition of alcohol, ether, or sodium hydroxide. If thymol is used instead of α-naphthol, a carmine-red colour is produced.

[illegible]

Tests for Albumoses.

1. Albumoses are not coagulated by heat.

2. Concentrated nitric acid precipitates the albumoses, but the precipitate is dissolved on being heated and reappears when cooled.

3. A saturated solution of picric acid precipitates albumoses; the precipitate is soluble on being heated and reappears when cooled.

4. Salicyl-sulphonic acid also precipitates albumoses: the

precipitate is dissolved when heated and reappears when cooled (McWilliam's Test).

5. *The Biuret Reaction.*—If to a solution of albumose a trace of 1 per cent. solution of copper sulphate is added, there is produced a bluish precipitate; on the addition of an excess of 20 per cent. caustic potash solution, a rose-red colour is produced. The colour is probably due to two CO—NH groups which are present.

6. The primary albumoses, proto-albumose and hetero-albumose, are precipitated by a solution of potassium ferrocyanide, if a few drops of 20 per cent. acetic acid have been previously added; secondary albumose, or deutero-albumose, is not so precipitated.

Tests for Peptone.

1. Peptone is not coagulated by heat, nor is it precipitated by nitric acid, picric acid, salicyl-sulphonic acid, or potassio-mercuric-iodide.

2. It gives the biuret reaction like the albumoses.

3. Peptone is precipitated by tannic acid and by alcohol, also by phospho-tungstic and phospho-molybdic acids.

The Action of Neutral Salts.

Magnesium sulphate or sodium sulphate to saturation, or half-saturation with ammonium sulphate, will precipitate globulins, meta-proteins, and the primary albumoses. Full saturation with ammonium sulphate will of course precipitate the globulins, meta-proteins, and the primary albumoses, but it will also precipitate albumins and the secondary albumoses. It will not precipitate peptones.

Indiffusibility of Proteins.

All proteins, except peptone and polypeptides, belong to the class of substances called colloids, because they pass with great difficulty, or not at all, through animal membranes. On the other hand, salts are termed crystalloids, as they are readily diffusible, and readily dialysable, that is, they readily pass through an animal membrane. If a colloidal solution of globulin in salt solution is placed in a dialyser, and the dialyser is placed in water, some of the water outside the

Tests for Proteins.

Reagent.	Albumin.	Globulin.	Infra-Protein.	Primary Albumoses.		Deutero-Albumose.	Peptone.
				Proto-Albumose.	Hetero-Albumose.		
Water	Soluble	Insoluble	Insoluble	Soluble	Insoluble	Soluble	Soluble
NaCl, 1 per cent. . .	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble
Saturation with NaCl or Na_2SO_4 or $MgSO_4$	Soluble	Insoluble	Insoluble	Insoluble	Insoluble	Soluble	Soluble
Half-saturation with $(NH_4)_2SO_4$	Soluble	Insoluble	Insoluble	Insoluble	Insoluble	Soluble	Soluble
Saturation with $(NH_4)_2SO_4$	Insoluble	Insoluble	Insoluble	Insoluble	Insoluble	Insoluble	Soluble
Heat	Coagulable	Coagulable	Not Coagulable	Not Coagulable	Not Coagulable	Not Coagulable	Not Coagulable

PRECIPITANTS OF PROTEINS.

Proteins in Solution may be precipitated by—	Protoeoses in Solution may be precipitated by—	Peptone in Solution may be precipitated by—
1. Strong HNO_3.	1. Strong HNO_3; this precipitate dissolves when heated and reappears when cooled.	...
2. Saturated solution of picric acid.	2. Saturated solution of picric acid; this precipitate dissolves when heated and reappears when cooled.	...
3. Acetic acid 20 per cent. and potassium ferrocyanide.	3. Primary proteoses are precipitated by 20 per cent. acetic acid and potassium ferrocyanide; this precipitate is soluble when heated and reappears when cooled.	...
4. Salts of heavy metals, which, with proteins, form metallic albuminates. Copper sulphate, silver nitrate, lead acetate, and mercuric chloride.	4. Salts of heavy metals.	...
5. Tannic acid.	5. Tannic acid.	Tannic acid.
6. Alcohol; after prolonged contact with alcohol the precipitate becomes coagulated (insoluble).	6. Alcohol, but the precipitate does not become coagulated.	Alcohol; this precipitate does not become coagulated.
7. Certain neutral salts.	7. Certain neutral salts.	...
8. Salicyl-sulphonic acid; on being heated the precipitate is coagulated.	8. Salicyl-sulphonic acid; when heated the precipitate dissolves and reappears when cooled.	Phospho-tungstic and by phosphomolybdic acid.

dialyser will osmose into the dialyser because of the osmotic pressure produced by the salt in solution inside. The salt, however, being a crystalloid, gradually dialyses out into the water outside the dialyser, and, if the outside water is changed sufficiently frequently, there will be practically no salt left in the dialyser, and in consequence the non-dialysable globulin will become precipitated.

CRYSTALLISATION OF PROTEINS.

At one time it was thought that proteins, as colloidal bodies, did not exist in a crystalline form. Later investigations have shown that this is not the case. "Aleurone" grains are crystalline bodies, which exist in the seeds of some plants such as hemp seeds and castor-oil seeds; these are protein in character.

Oxyhæmoglobin and some of its derivatives can be crystallised. Egg-albumin and serum-albumin crystals have been produced as follows:—

The solution, containing the egg-albumin and egg-globulin, or the serum-albumin and serum-globulin, is shaken with an equal volume of a saturated solution of ammonium sulphate. The mixture must be allowed to stand for a few hours. The globulin is precipitated and this is filtered off. The filtrate is allowed to evaporate very slowly, when small clumps of crystals are thrown down. If a little acetic acid or sulphuric acid is added, the crystals appear more rapidly. Only a few of the proteins, however, have been obtained in crystalline form.

HEAT COAGULATION OF PROTEIN SOLUTIONS.

The heat coagulation point is an important factor in distinguishing between different proteins, and the process of separating soluble proteins in mixtures by means of fractional heat coagulation is frequently employed.

COAGULATION TEMPERATURE OF SOME OF THE PROTEINS.

Proteins of Blood.	Fibrinogen	56° C.
	Serum-globulin	75° C.
	Serum-albumin	73°–86° C.
	Hæmoglobin	64° C.
Proteins of Muscle.	Paramyosinogen	47° C.
	Myosinogen	56° C.
	Myoglobulin	63° C.
	Myoalbumin	70–73° C.

Crystallin	63–72° C.
Egg-albumin	56° C.
Lact-globulin	72° C.

Bence-Jones' proteose when in solution becomes precipitated when heated to 50°–58° C.; on further raising the temperature the precipitate becomes redissolved.

Optical Rotation of Protein Solutions.

Solutions of proteins are optically active. Most animal proteins are lævo-rotatory; hæmoglobin and the nucleo-proteins are dextro-rotatory. Plant proteins are lævo-rotatory.

Osmotic Pressure Exerted by Proteins in Solution.

In his researches upon the function of the kidney glomeruli, Starling measured the osmotic pressure exerted by a serum solution of known protein content. An osmometer is generally employed for measuring the osmotic pressure of colloids. Weymouth Reid has shown that proteins, which have been very well washed, have practically no osmotic pressure, and he attributes the osmotic pressure of protein solutions, recorded by others, to the adsorbed inorganic substances. Moore, on the other hand, maintains that proteins do exert a definite osmotic pressure, but that their state of aggregation varies in solutions which contain different quantities of salt.

CHAPTER IV.

CARBOHYDRATES.

THE carbohydrates, such as starch and cane sugar, occur chiefly in vegetable tissues, though some are found in animal tissues; for example, glycogen occurs in the liver cells, in the cells of the placenta, and in muscle; dextrose in the blood plasma; and lactose in milk.

Carbohydrates are formed in plant cells from CO_2 and H_2O. In all probability formaldehyde is the first product of the biotic activity of plant cells, the carbon dioxide, which is absorbed from the air, and the water obtained through the root being converted (condensed) into CH_2O by the combined influence of sunlight and chlorophyll. The formaldehyde is converted into glucose, and this is further converted into starch. This synthesis is probably brought about by the action of enzymes contained within the vegetable cells.

If a primary alcohol is oxidised an aldehyde is produced, thus—

$$\underset{\text{(Ethyl alcohol)}}{CH_3.CH_2.OH} + O = \underset{\text{(Acetic aldehyde)}}{CH_3.COH} + H_2O$$

the COH is the aldehyde group, and may be readily oxidised to form an acid, thus—

$$\underset{\text{(Acetic aldehyde)}}{CH_3.COH} + O = \underset{\text{(Acetic acid)}}{CH_3.COOH}$$

A secondary alcohol is one in which the OH group and one H atom are attracted to the same C atom, and the typical group is therefore the divalent radical $>CH.OH$. When this is oxidised, the first oxidation product is a ketone, which contains the group $>CO$, thus—

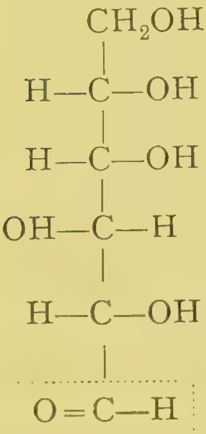
$$\underset{\text{(Secondary propyl alcohol)}}{CH_3.CHOH.CH_3} + O = \underset{\text{(Propyl-ketone or acetone)}}{CH_3.CO.CH_3} + H_2O$$

A primary alcohol contains the group OH, aldehyde the group $O=C-H$, secondary alcohol the group $CH.OH$, and ketone the group $>CO$.

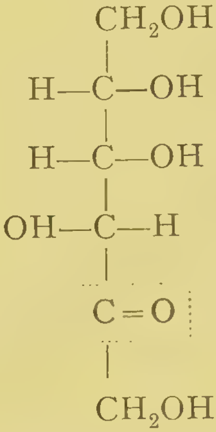
The simplest carbohydrates are aldehydes or ketones of the hexatomic alcohols, so called because they contain six OH groups.

The more important hexatomic alcohols are sorbite, mannite, and dulcite, which have the empirical formula $C_6H_8(OH)_6$.

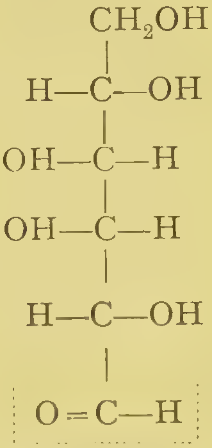
By oxidation of these alcohols, their aldehydes and ketones may be obtained. Dextrose is the aldehyde of sorbite, mannose is the aldehyde of mannite, lævulose is the ketone of mannite, galactose is the aldehyde of dulcite.



Dextrose
(an aldehyde)



Lævulose or fructose
(a ketone)



Galactose
(an aldehyde)

The sugars, which are aldehydes, are called aldoses; those which are ketones are called ketoses. These sugars are reducing agents, and become oxidised to organic acids. The simple sugars contain C six times, hence they are called hexoses. The more important are dextrose, lævulose, and galactose, named the monosaccharides. If two molecules of a monosaccharide combine with the loss of one molecule of water, a disaccharide is obtained, thus—

$$C_6H_{12}O_6 + C_6H_{12}O_6 - H_2O = C_{12}H_{22}O_{11}$$

If more than two molecules of the monosaccharides lose water, and undergo further condensation, a polysaccharide is obtained, thus—

$$nC_6H_{12}O_6 - nH_2O = (C_6H_{10}O_5)n$$

A pentose, *i.e.* a sugar containing C five times, has been obtained from nucleic acid, which occurs in the cells of the pancreas and liver. Pentoses given to an animal in its food are excreted unchanged in the urine.

TABLE OF CARBOHYDRATES.

Monosaccharides (Glucoses) $C_6H_{12}O_6$.	Disaccharides (Sucroses) $C_{12}H_{22}O_{11}$.	Polysaccharides (Amyloses) $(C_6H_{10}O_5)$ n.
+52°·5 Dextrose (R.).	+67° Cane sugar (Non-R.).	+Starch.
−92° Lævulose (R.).	+140° Maltose (R.).	+Erythro-dextrin.
+83° Galactose (R.).	+52°·5 Lactose (R.).	+Achroö-dextrin.
		+Glycogen.
		+Cellulose.

+ indicates that these carbohydrates are dextro-rotatory.
− ,, this is lævo-rotatory.
R. ,, these are reducing sugars.
Non-R. ,, this is a non-reducing sugar.

TESTS FOR THE REDUCING SUGARS.

Trommer's Test.—Add to the sugar solution a few drops of copper sulphate solution and a little 20 per cent. caustic potash; a blue precipitate is formed, which re-dissolves in the sugar solution. Boil the blue solution; a brick-red precipitate (cuprous oxide) or a yellow precipitate forms (cuprous hydrate).

Fehling's Test.—Boil the Fehling's solution [which consists of a solution of copper sulphate, sodium hydrate, and potassium sodium tartrate (Rochelle salt)] in order to ascertain if it retains its clear blue colour. If the solution remains clear blue after boiling, add the solution of sugar and boil again; a precipitate of cuprous oxide or cuprous hydrate falls.

Johnson's Test.—To the sugar solution add a few drops of a saturated solution of picric acid and a little 20 per cent. caustic potash. On being boiled, the picric acid is reduced to picramic acid, which forms a dark red solution almost black.

Moore's Test.—To a solution of dextrose add half its volume of 20 per cent. caustic potash, and boil; the solution turns brown. Add to this some 25 per cent. H_2SO_4; an odour of caramel may be detected.

Molisch's Reaction.—Add to a dextrose solution a little α-naphthol dissolved in alcohol, and allow a few drops of concentrated H_2SO_4 to run to the bottom of the test tube; a purple ring forms at the surface of contact. This test is given by those proteins which contain a carbohydrate radical as well as by all carbohydrates.

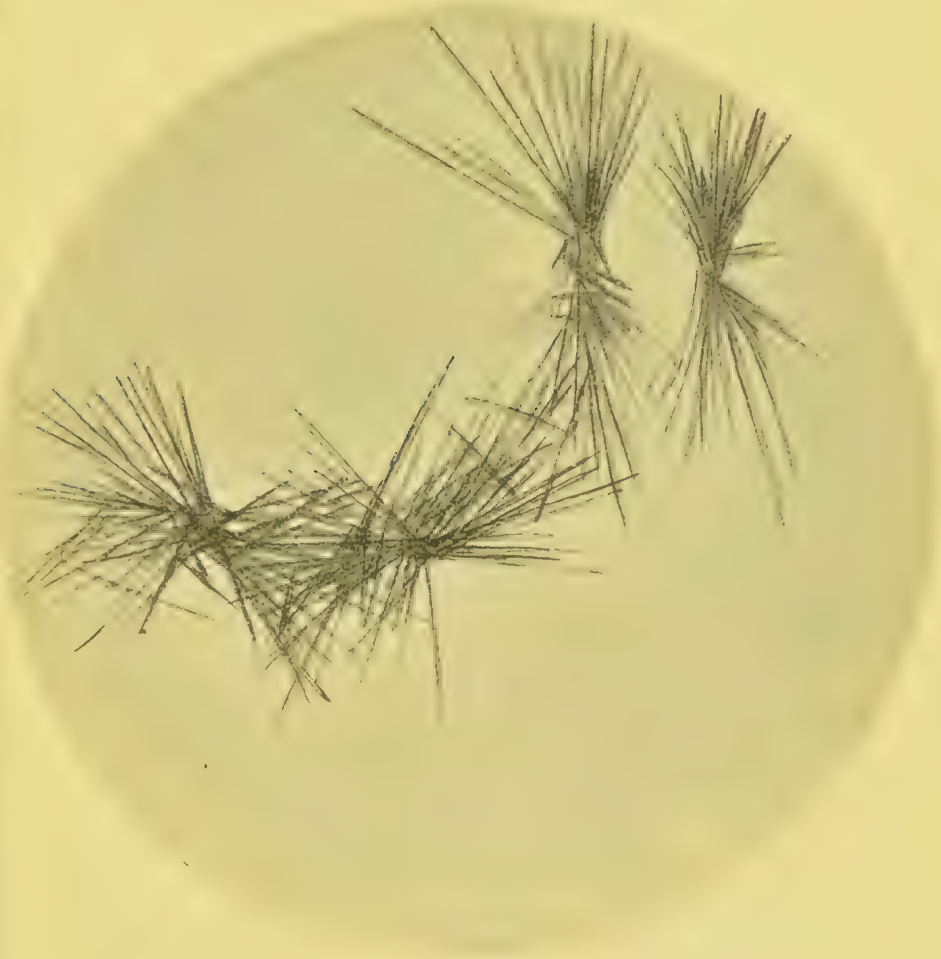


FIG. 2.—Crystals of Phenyl-glucosazone. (*After* Halliburton.)

Phenyl-Hydrazine Test.—Take about half a test tube of the sugar solution and add 1 decigramme of phenyl-hydrazine hydrochloride and 2 decigrammes of sodium acetate, and heat in a water bath at 100° C. for half an hour. On cooling, sometimes before, a yellow crystalline or amorphous precipitate

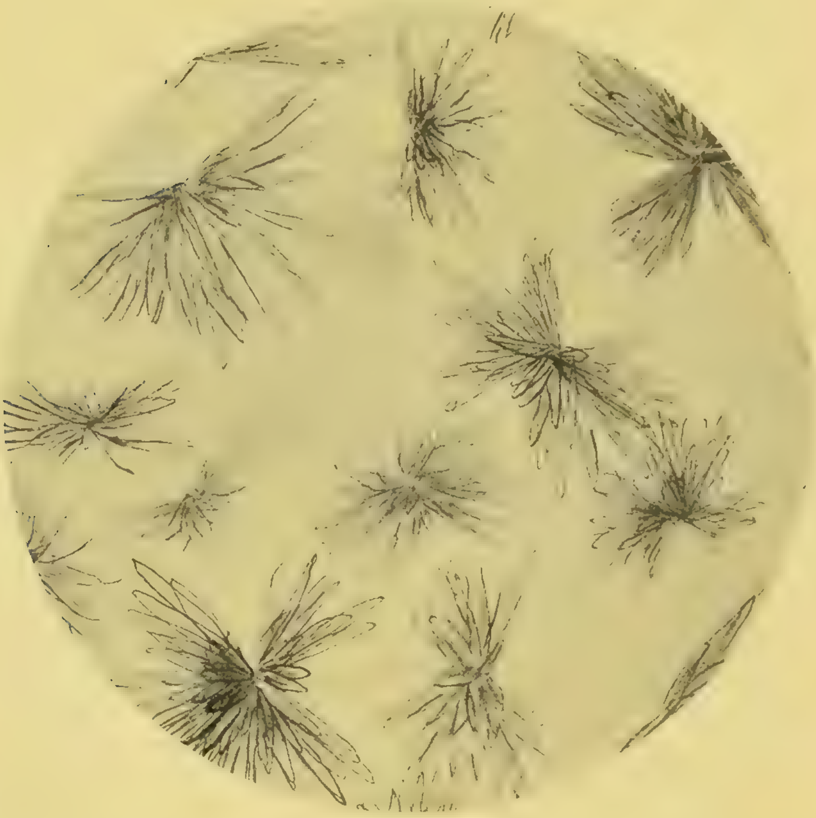


FIG. 3.—Crystals of Phenyl-maltosazone. (*After* Halliburton.)

separates out. If the precipitate is amorphous, it should be dissolved in hot alcohol, water added, and then further boiled to drive off the alcohol; the osazone crystals will then separate out.

Dextrose and lævulose give a precipitate of phenyl-glucosazone, which consists of bundles of needle-shaped crystals melting at 208° C. Galactose yields phenyl-galactosazone, melting at 193° C. Maltose yields phenyl-maltosazone which crystallises in wide needles, melting at 206° C.; these are readily soluble in hot alcohol, and in boiling water.

Lactose yields phenyl-lactosazone, which forms clusters of fine needle-shaped crystals melting at 200° C. It is soluble in 80–90 parts of boiling water.

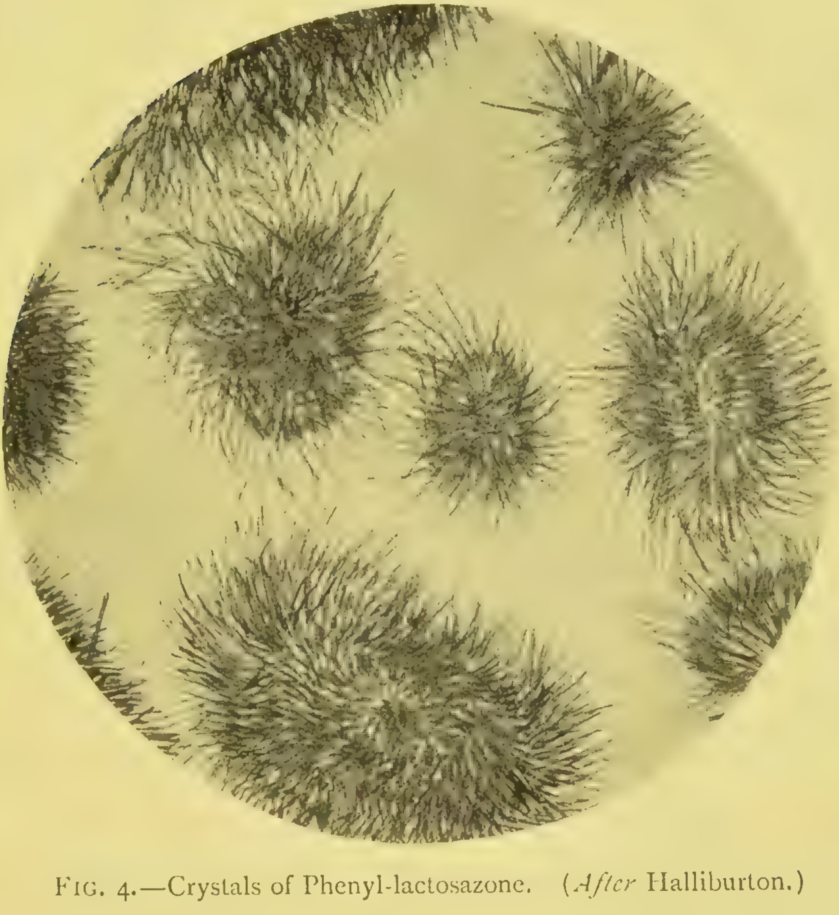


FIG. 4.—Crystals of Phenyl-lactosazone. (*After* Halliburton.)

Fermentation Test.—To a solution of dextrose in a test tube add a little dried yeast. The test tube should then be filled by adding mercury, and inverted over a trough containing mercury. The whole should be kept at body temperature for twenty-four hours. The zymase of the yeast splits the sugar into CO_2 and $C_2H_5.OH$; the former collects in the upper part of the test tube.

$$C_6H_{12}O_6 = 2C_2H_5.OH + 2CO_2$$

TESTS FOR CANE SUGAR (*a Non-Reducing Sugar*).

(*a*) If a few drops of copper sulphate solution and some 20 per cent. caustic potash are added to a solution of cane sugar, a clear blue solution remains, and is unaltered by boiling.

(*b*) Boil a solution of cane sugar with a few drops of 25 per cent. H_2SO_4 for five minutes. The cane sugar is hydrolysed into equal parts of dextrose and lævulose, both of which are reducing sugars.

(*c*) Add to a solution of cane sugar an equal volume of concentrated HCl and boil; a reddish tinge is produced, which is converted into a deep red colour by prolonged boiling.

(*d*) Add to the cane-sugar solution a few drops of an alcoholic solution of α-naphthol and 5 c.c. concentrated HCl and boil; a purple colour is produced (Molisch's reaction).

Cane sugar forms no compounds with phenyl-hydrazine.

Dextrose or Grape Sugar.—This sugar occurs in fruits, honey, blood plasma (0·12 to 0·2 per cent.), cerebro-spinal fluid, and muscles. In some forms of diabetes mellitus it is present in blood plasma in quantity more than 0·2 per cent., a condition known as hyperglycæmia, and is consequently excreted in the urine.

It is soluble in cold and hot water, and in alcohol. It forms crystals, and is less sweet than cane sugar. In alkaline solutions it is a reducing agent, and will in consequence reduce salts of copper, bismuth, and silver.

Dextrose may be estimated by standard Fehling's solution, the fermentation test, and by its specific rotation by the polarimeter. Dextrose may be readily prepared by boiling starch with *dilute* sulphuric acid.

Lævulose.—This is present in small quantities in the blood in the portal vein. It may be crystallised with difficulty. Cane sugar, when heated with dilute mineral acids, such as H_2SO_4, is converted into dextrose and lævulose.

Invertase in the succus entericus and the zymase of yeast will bring about the same change—

$$\underset{\substack{\text{(Cane sugar)}\\+}}{C_{12}H_{22}O_{11}} + H_2O = \underset{\substack{\text{(Dextrose)}\\+}}{C_6H_{12}O_6} + \underset{\substack{\text{(Lævulose)}\\-}}{C_6H_{12}O_6}$$

The dextro-rotatory cane sugar is converted into a mixture of a dextro-rotatory sugar, and a lævo-rotatory sugar, the two together being lævo-rotatory, for the lævo-rotatory power of the lævulose is greater than the dextro-rotatory power of the dextrose. This change is called inversion, and the product of the change is invert sugar. Invert sugar is sweeter than cane sugar.

Galactose.—If lactose is treated with a dilute solution of mineral acid, it is converted into dextrose and galactose. The same change is brought about by the enzyme, lactase, which exists in the succus entericus. Galactose is a constituent of the cerebrosides, phrenosin and kerasin, which are found in brain tissue.

Cane Sugar.—This is found in the juices of fruits and certain plants. Cane sugar is a non-reducing sugar, but, by boiling cane sugar with dilute mineral acid, it is converted into the reducing sugars, dextrose and lævulose; a similar change occurs in the alimentary canal by the action of invertase or sucrase of the succus entericus.

Yeast cells, by the invertase which they produce, convert cane sugar into dextrose and lævulose, and these sugars are further acted upon by the zymase, also produced by the cells, and converted into alcohol and CO_2, thus—

$$\begin{aligned} C_{12}H_{22}O_{11} + H_2O &= C_6H_{12}O_6 + C_6H_{12}O_6 \\ C_6H_{12}O_6 &= 2C_2H_5OH + CO_2 \end{aligned}$$

Lactose.—This is found in milk and, occasionally, in the blood and urine of women in the early days of lactation, or after the weaning of the child has commenced. It forms rhombic crystals and is slightly sweet. Lactose is insoluble in alcohol and ether. By boiling with weak mineral acid, by the action of yeast, and by the action of lactase contained in the succus entericus, lactose is converted into dextrose and galactose, thus—

$$\underset{\text{(Lactose)}}{C_{12}H_{22}O_{11}} + H_2O = \underset{\text{(Dextrose)}}{C_6H_{12}O_6} + \underset{\text{(Galactose)}}{C_6H_{12}O_6}$$

only those torulæ which contain lactase are capable of fermenting lactose.

The souring of milk is due to enzymes produced by micro-organisms acting upon lactose, and producing the following change:—

$$\underset{\text{(Lactose)}}{C_{12}H_{22}O_{11}} + H_2O = \underset{\text{(Lactic acid)}}{4C_2H_5O.COOH}$$

Maltose.—If starch is boiled with a dilute mineral acid, or acted on by malt diastase, maltose is produced. If starch is digested by the enzyme, ptyalin of the saliva, or the enzyme, amylopsin of the pancreatic juice, it is converted into maltose.

Maltose, by boiling with dilute mineral acid or by the action of maltase of the succus entericus, is converted into dextrose, thus—

$$\underset{\text{(Maltose)}}{C_{12}H_{22}O_{11}} + H_2O = \underset{\text{(Dextrose)}}{2C_6H_{12}O_6}$$

Maltose is fermented only by yeasts which contain maltase, and then not until the enzyme has first produced dextrose.

RELATIVE REDUCING POWER OF THE SUGARS.

10 c.c. of Fehling's solution are reduced by 0·05 grm. dextrose.
10 c.c. ,, ,, ,, 0·07 ,, lactose.
10 c.c. ,, ,, ,, 0·08 ,, maltose.

ENZYME ACTION UPON SUGARS.

Disaccharides may be hydrolysed by mineral acids into the monosaccharides, a process which requires a high temperature, and an appreciable amount of time. Enzymes, on the other hand, are far more active catalysts or hydrolysing agents. A very small quantity of an enzyme, acting at the body temperature, is far more powerful than a strong mineral acid acting at a high temperature. The enzymes, which hydrolyse the sugars, exhibit a selective action, whereas hydrolysis, produced by mineral acids, is general in character. Invertase or sucrase hydrolyses cane sugar into dextrose and lævulose, lactase hydrolyses lactose into dextrose and galactose, and maltase hydrolyses maltose into dextrose. Lactase has no action upon maltose, and maltase has no action upon lactose.

Croft Hill pointed out that enzymes have a reversible or synthetical action. "The manner of the synthesis by enzymes is a matter of dispute. It is urged, on the one hand, that enzymes produce by synthesis the same bodies which they hydrolyse; on the other hand, it is suggested that the action of the enzyme is restricted to the formation of a compound isomeric with that normally hydrolysed by the enzyme. A third view is, that altogether distinct enzymes effect the synthesis" (Armstrong).

Maltase will hydrolyse maltose into dextrose, but Armstrong has shown that the main product in the case of the action of yeast extract (maltase) on glucose is not maltose, but isomaltose.

Starch.—This is found in vegetable cells. Each starch grain has a central hilum, around which there are alternate layers of starch granulose and starch cellulose. Starch is insoluble in cold water. It is soluble in boiling water, producing a bluish opalescent solution. A solution of starch gives a deep blue colour with a weak solution of iodine; on being warmed the colour disappears (dissociation), and, provided that the warming has not driven off all the iodine, the colour reappears when the solution is cooled, though it is not so intense as before. If starch solution is boiled with dilute mineral acids, it is converted into soluble starch $(C_6H_{10}O_5)_{200}$, which forms a clear solution; then erythrodextrin and achroö-dextrin are produced, and finally dextrose. The ptyalin of the saliva, and the amylopsin of the pancreatic juice produce similar changes, the end products being achroö-dextrin and maltose, thus—

Starch
|
Soluble starch
|
Erythro-dextrin
and
Achroö-dextrin
|
Achroö-dextrin and maltose.

Dextrin is formed from starch, and is amorphous and gummy. It is soluble in cold water, producing a clear solution; it is precipitated by alcohol (85 per cent.) and ether. It is a non-reducing substance and will not ferment. It can be hydrolysed into dextrose. Erythro-dextrin gives a deep red-brown colour with a weak solution of iodine; the colour disappears when the solution is warmed and reappears when it is cooled, whereas achroö-dextrin gives no characteristic colour with a solution of iodine.

Glycogen.—This is sometimes called animal starch. It is present in the liver cells, in striped and unstriped muscle, and is relatively abundant in cardiac muscle. It is found in the testicle, in white blood corpuscles and in the placenta. Pure glycogen is a white amorphous powder, tasteless, soluble in cold water, producing a greenish opalescent solution. It is insoluble in ether, and precipitated by 55 per cent. alcohol. It is a non-reducing substance. With a solution of iodine, it gives a red-brown colour, which disappears on being warmed, but the colour reappears when cooled.

	Glycogen.	Dextrin.
In cold water . .	Opalescent solution.	Clear solution.
Alcohol . . .	Precipitated by 55 per cent.	Precipitated by 85–95 per cent.
Basic lead acetate .	Precipitated.	Precipitated after the addition of ammonia.
Saturation with $(NH_4)_2SO_4$.	Precipitated.	Erythro-dextrin is partially precipitated. Achroö-dextrin is not precipitated.

Preparation of Glycogen.—This is obtained from a rabbit.

(*a*) The animal is fed on a diet rich in carbohydrate, such as carrots, for six hours before it is killed. The quickest method of killing is by sharply striking the animal on the back of the neck, while it is being held by its hind limbs.

(*b*) The abdomen and thorax must be rapidly opened, and a cannula placed in the portal vein, and another in the inferior vena cava in the thorax.

(*c*) Normal salt solution is run through the cannula in the portal vein; the liver at first swells, and then gradually becomes pale through the blood being washed out.

(*d*) The liver should be quickly removed and the gall bladder cut out.

(*e*) The liver is then cut into small pieces, and thrown into boiling water which has been previously acidulated with acetic acid. The proteins of the liver are coagulated, the enzymes present killed, and some glycogen is extracted by the boiling water.

(*f*) Small pieces of the scalded liver are then ground up in a mortar with powdered glass, and extracted with boiling water.

(*g*) The whole must be carefully filtered, when the glycogen will be found in opalescent solution in the filtrate.

(*h*) The filtrate must be evaporated slowly in order that it may be concentrated.

(*i*) To the concentrated solution, alcohol, up to 55 per cent., is added; this precipitates the glycogen, which may be collected and dried.

Cellulose.—This is the material of which the cell walls of vegetable cells and fibres of plants are composed. It is insoluble in water. By boiling it for a long period with mineral acids, it is converted into glucose. It resists the action of digestive enzymes. Boiling, however, ruptures the cellulose capsule of starch grains. Much of the cellulose of the food passes through the alimentary canal unchanged.

Pentoses ($C_5H_{10}O_5$).—Only two pentoses are known to occur naturally, namely, *xylose*, which occurs in straw, and *arabinose*, which occurs in gum. In the animal kingdom, however, pentoses form an important constituent of nucleoproteins and nuclein. The pentoses are not fermented by enzymes.

ACTION OF NITRIC ACID ON THE CARBOHYDRATES.

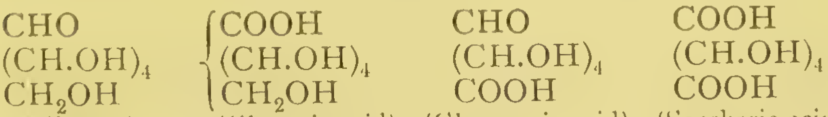
If solutions of the carbohydrates are heated with nitric acid, they become oxidised and yield certain acids, thus—

Galactose yields mucic acid ($C_6H_{10}O_8$) (insoluble).

Dextrose, cane sugar, maltose, dextrins, and starch yield saccharic acid (soluble).

Lactose yields saccharic acid and mucic acid.

On oxidation, glucose gives rise to three acids as follows:—



$$\begin{array}{l} CHO \\ (CH.OH)_4 \\ CH_2OH \end{array} \quad \left\{ \begin{array}{l} COOH \\ (CH.OH)_4 \\ CH_2OH \end{array} \right. \quad \begin{array}{l} CHO \\ (CH.OH)_4 \\ COOH \end{array} \quad \begin{array}{l} COOH \\ (CH.OH)_4 \\ COOH \end{array}$$

(Glucose) (Gluconic acid) (Glycuronic acid) (Saccharic acid)

In normal circumstances, the glucose in the body is readily oxidised to carbon dioxide and water. "When certain substances, such as chloral or camphor, which are oxidised in the body only with difficulty, are brought into the system, the organism has the power of combining them with glucose to form *glucosides*. In such compounds one end of the glucose molecule is shielded from attack, but oxidation takes place at the other extremity of the molecule, and a glycuronic acid derivative is formed" (Armstrong). This is excreted in the urine. Armstrong also states that the faculty of removing injurious substances from circulation in combination with glucose seems to be common to both the animal and vegetable kingdoms, and the glucosides in the plant may be compared with the glycuronic acid derivatives in the animal.

Glucosides.—The term glucosides is applied to a large number of bodies, all of which have a common property, namely, that when they are hydrolysed by acids they yield a *glucose* and one or more other products. The glucosides occur in plants, especially in the fruit, bark, and roots, and the sugar present is in most cases dextrose. It has been already stated that these glucosides correspond, to a certain extent, with the glycuronic acid derivatives which sometimes occur in the urine as the result of taking camphor, chloroform, etc. Some of the best-known glucosides are amygdalin of the almond and salicin of the willow. Phloridzin is a glucoside found in the bark of apple, pear, and cherry trees. When administered internally it produces glycosuria. Mineral acids hydrolyse phloridzin into glucose and phloretin ($C_{15}H_{14}O_5$), the latter of which, when administered, also causes glycosuria.

CHAPTER V.

FATS.

FAT is found deposited in certain of the connective-tissue cells of the body forming adipose tissue. The chief fat depôts are the subcutaneous tissue, the omentum, and the yellow and red bone marrow, but it is present in small quantities in most of the tissues. It is also present in the form of an emulsion in milk.

Chemically, the fats of the body consist of three neutral fats in varying proportions. They are as follows :—

Triolein melts at – 5° C.
Tripalmitin melts at 45° C.
Tristearin melts at 53–65° C.

At the body temperature (38° C. or 99° F.) the triolein holds the tripalmitin and tristearin in solution. Fats are insoluble in water, but soluble in hot alcohol, ether, and chloroform.

CHEMICAL CONSTITUTION OF FATS.

The neutral fats may be split into the substances of which they are composed, namely, into glycerin and the corresponding fatty acid; this change may be brought about by the action of superheated steam, mineral acids, and by the action of certain enzymes, such as gastric lipase and pancreatic lipase.

$$\underset{\text{(Triolein)}}{C_3H_5(O.C_{17}H_{33}.CO)_3} + 3H_2O = \underset{\text{(Glycerin)}}{C_3H_5(OH)_3} + \underset{\text{(Oleic acid).}}{3C_{17}H_{33}COOH,}$$

$$\underset{\text{(Tripalmitin)}}{C_3H_5(O.C_{15}H_{31}.CO)_3} + 3H_2O = \underset{\text{(Glycerin)}}{C_3H_5(OH)_3} + \underset{\text{(Palmitic acid).}}{3C_{15}H_{31}.COOH,}$$

$$\underset{\text{(Tristearin)}}{C_3H_5(O.C_{17}H_{35}.CO)_3} + 3H_2O = \underset{\text{(Glycerin)}}{C_3H_5(OH)_3} + \underset{\text{(Stearic acid).}}{3C_{17}H_{35}COOH,}$$

The insoluble fatty acid may be converted into a soluble soap by the replacement of the H of the acid radical by K or

Na of the KOH or NaOH used. In the case of palmitic acid, potassium palmitate is formed, thus—

$$C_{15}H_{31}COOH + KOH = C_{15}H_{31}COOK + HOH.$$

Oleic Acid is a product of oxidation of alcohols belonging to the acrylic acid series, the first member of the group is allyl alcohol ($CH_2 : CH.CH_2OH$), its aldehyde being acrolein ($CH_2 : CH.OCH$), and its acid, acrylic acid ($CH_2 : CH.COOH$ or $C_2H_3.COOH$). The general formula of this series of *unsaturated* fatty acids is $C_{n-1}H_{2n-3}.COOH$, and oleic acid, which is the eighteenth member in the acrylic acid series, has the composition $C_{17}H_{33}COOH$.

Palmitic Acid and **Stearic Acid** belong to the fatty acids derived from the primary monatomic alcohols by oxidation, thus—

$CH_3.OH$, Methyl alcohol; $H.OCH$, Formic aldehyde; $H.COOH$, Formic acid.

$C_2H_5.OH$, Ethyl alcohol; $CH_3.OCH$, Acetic aldehyde; CH_3COOH, Acetic acid.

$C_3H_7.OH$, Propyl alcohol; $C_2H_5.OCH$, Propylic aldehyde; $C_2H_5.COOH$, Propionic acid.

$C_4H_9.OH$, Butyl alcohol; $C_3H_7.OCH$, Butyric aldehyde; $C_3H_7.COOH$, Butyric acid.

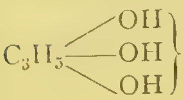
$C_5H_{11}.OH$, Amyl alcohol; $C_4H_9.OCH$, Valeric aldehyde; $C_4H_9.COOH$, Valeric acid.

The sixteenth aldehyde in the series is palmitic aldehyde, $C_{15}H_{31}OCH$, which, on oxidation, yields palmitic acid, $C_{15}H_{31}COOH$; the eighteenth aldehyde in the series is stearic aldehyde, $C_{17}H_{35}.OCH$, which, on oxidation, yields stearic acid, $C_{17}H_{35}.COOH$. The general formula of this series is $C_{n-1}H_{2n-1}.COOH$; these are saturated fats, and therefore have no reducing action.

The following are the important fatty acid radicals:—

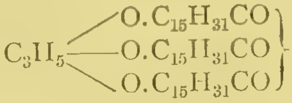
CH_3CO, Acetyl, the radical of acetic acid.
$C_{15}H_{31}CO$, Palmityl, the radical of palmitic acid.
$C_{17}H_{35}CO$, Stearyl, the radical of stearic acid.
$C_{17}H_{33}CO$, Oleyl, the radical of oleic acid.

Glycerin or **Glycerol** is a triatomic alcohol, $C_3H_5(OH)_3$, and the H of the hydroxyl group may be replaceable by organic acid radicals, and, in the case of the neutral fats, each of the three hydrogen atoms of the hydroxyl groups may be replaced by the radicals of the fatty acid, thus—



$$C_3H_5\left\langle\begin{array}{l}OH\\OH\\OH\end{array}\right\}$$

Glycerin



$$C_3H_5\left\langle\begin{array}{l}O.C_{15}H_{31}CO\\O.C_{15}H_{31}CO\\O.C_{15}H_{31}CO\end{array}\right\}$$

The Neutral Fat Tripalmitin.

EMULSIFICATION.

During the digestion of fats, the small particles of fat are finely divided, and each fat globule is surrounded by a fine coating of protein, which prevents the globules from running together to form an oil. The process of emulsification is purely a physical one, and, during digestion, takes place chiefly in the duodenum.

Emulsification is brought about by a number of factors working together—

1. The presence of the gluco-protein, mucin.
2. The alkalinity of the pancreatic juice.
3. The presence of the bile salts, sodium glycocholate and sodium taurocholate.
4. The movement and warmth of the intestines aid the process.

TESTS FOR FATTY ACIDS.

Phenolphthalein Reaction.—A few drops of phenolphthalein are to be added to a little water containing a drop of 20 per cent. caustic potash; this produces a red solution. If a drop of this red solution is added to a solution of fatty acid, the red colour is at once discharged.

Osmic Acid Test.—Fatty material containing triolein or oleic acid, both unsaturated bodies, will reduce osmic acid to a lower oxide of osmium, which is black. Tripalmitin and tristearin are saturated fats, and are therefore unable to reduce osmic acid.

Test for Glycerin.—Mix the glycerin (or a fat such as lard) with powdered $KHSO_4$, and heat strongly; the odour of acrolein, or acrylic aldehyde, is perceived (it causes the offensive smell of smouldering tallow candles).

$$C_3H_5(OH)_3 = C_2H_3.OCH + 2H_2O$$

The acrolein will blacken filter paper previously moistened with a solution of silver nitrate and ammonia.

Lipochromes or **Luteins** are yellow fatty pigments, which occur in the fats of milk, in the fat of the yolk of eggs, and in the fats of connective tissue. They also are found in blood plasma and in serous fluids. Lipochromes, like the fats themselves, contain no nitrogen.

CHAPTER VI.

THE LIPOIDS.

Lipoids are fatty substances which occur, with the proteins, in the protoplasm of the cells of the body. Like the proteins, their molecules are labile in character. The lipoids are found abundantly in nervous tissues; they exist in blood corpuscles, in bile, and, for the most part, are present mixed with fats in the ether-alcohol extract of the tissues. There are three chief groups—

1. Cholesterins.
2. Galactosides.
3. Phosphatides.

I. THE CHOLESTERINS OR CHOLESTEROLS.

These substances, like the fats, consist of C.H.O.

Cholesterin or **Cholesterol** ($C_{27}H_{45}.OH$) belongs to the terpene series; it contains five reduced benzine rings linked together with a double linkage at the end of an open chain. It is insoluble in water, but is freely soluble in ether, chloroform, acetone, and boiling alcohol. It is present in the medullary sheath of nerves, and is especially abundant in the free state in the brain, from which it can be readily extracted by cold acetone. It is present in the blood corpuscles. Bile contains small quantities, and it is present in gall stones, either with bilirubin calcium, or in the free state. It is also present in the spleen. Its abundance in the tissues suggests that it has some protective action, by means of which the tissue cells are protected against the action of those toxins which are liable to enter the body through the alimentary canal, or through the skin. This may be the reason why there is cholesterin in the envelope of the coloured blood corpuscles, and its presence there is, in all probability, to prevent hæmolysis or destruction of the coloured blood corpuscles by toxins, which may have entered the body as just stated, and those also, produced by micro-organisms which have gained access to the blood. Cholesterin exists combined with fatty acids forming esters in the cortical part of the suprarenal capsules. These esters are cholesterin palmitate, cholesterin oleate, and cholesterin stearate.

TESTS FOR CHOLESTERIN.

1. Cholesterin forms rhombic plates, which chip readily, and often appear to have a piece off the corner. These crystals have one molecule of water of crystallisation.

2. If cholesterin crystals, to which a drop of sulphuric acid and a trace of water have been added, are gently heated on a slide, their margins turn red, and the crystals soon lose their crystalline form.

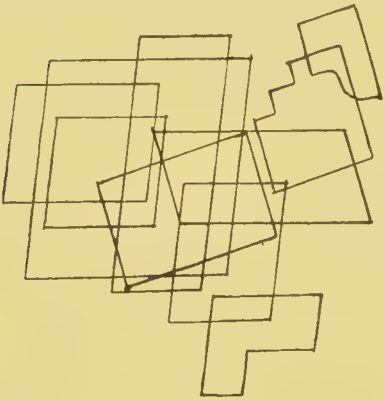


FIG. 5.—Crystals of Cholesterin.

3. *Salkowski's Test.*—A solution of cholesterin is made in chloroform, and then poured gently on to a little concentrated H_2SO_4 contained in a previously *dry* test tube. At the junction of the two a brilliant red ring forms, and, on being gently shaken, the red colour diffuses through the chloroform solution, and the subjacent acid acquires a greenish tint.

4. *Liebermann's Test.*—To a chloroform solution of cholesterin a few drops of acetic anhydride are added, and then gently shaken in a previously *dry* test tube. On the careful addition of a few drops of concentrated sulphuric acid, a red colour is produced, which turns blue, then bluish-green. The colour disappears on a trace of moisture being added, but reappears on the addition of more concentrated sulphuric acid.

5. Cholesterin in solution, in ether, or chloroform, is lævo-rotatory and melts at 145° C.

Iso-cholesterin is found in sebum, the secretion of the sebaceous glands, and is present in large quantity in lanoline, a preparation of sheep's wool fat. It forms crystals similar to those of cholesterin, and these give the red colour when warmed with H_2SO_4 and water. It does not give Salkowski's, but it does give Liebermann's reaction (Hammarsten). It is, however, dextro-rotatory when in solution. It melts at 138° C.

Phyto-cholesterins (Phyto-sterins) are the cholesterins of plants, and are isomeric with the animal cholesterins.

II. THE GALACTOSIDES (NITROGENOUS GLUCOSIDES OR CEREBROSIDES).

These substances consist of C.H.O.N., and, when broken up, yield galactose ($C_6H_{12}O_6$). The galactosides occur in brain substance, and constitute about 70 per cent. of the substance originally known as protagon. The two galactosides are phrenosin (cerebrin) and kerasin.

Phrenosin or **Cerebrin** is a white crystalline substance, soluble in glacial acetic acid, and yields three substances on hydrolysis—

1. Galactose.
2. A base called sphingosine.
3. An oxyacid of a fatty nature, called neuro-stearic acid.

Kerasin is a waxy substance, insoluble in ether, but soluble in warm alcohol. On hydrolysis it yields—

1. Galactose.
2. Sphingosine.
3. A fatty acid, not neuro-stearic acid.

Nothing is known with regard to the significance of these substances, although Abderhalden suggests that they may represent a form, in which sugar may be stored in safety, and so protected against oxidation.

III. THE PHOSPHATIDES.

These substances contain C.H.O.N.P., and are characterised by possessing the following properties:—

1. They have a fatty acid radical.
2. They contain an alcohol, glycerin.
3. On hydrolysis, the phosphorus is split off as phosphoric acid.
4. They are labile bodies which become oxidised with great ease.

The phosphatides are classified according to the proportion of N. and P. in their molecules, thus—

(*a*) Monoamino-mono-phosphatides, 1 N. to 1 P. (lecithin, kephalin).
(*b*) Diamino-mono-phosphatides, 2 N. to 1 P. (sphingo-myelin, jecorin).
(*c*) Monoamino-diphosphatides, 1 N. to 2 P. (cuorin which has been obtained from the heart).
(*d*) Diamino-diphosphatides, 2 N. to 2 P.
(*e*) Triamino-mono-phosphatides, 3 N. to 1 P.

Lecithin ($C_{42}H_{84}NPO_3$) is usually found with cholesterin in the medullary sheath of nerves, in blood corpuscles, and, in small quantities, in the bile. It is a yellow waxy-like body, soluble in alcohol and ether, but insoluble in acetone.

It gives the following reactions :—

1. Treated with osmic acid, it turns slightly black in colour.

2. When heated with potassium hydrogen sulphate ($KHSO_4$) in a test tube, acrolein ($CH_2 : CH.CHO$) is evolved, and may be tested for, first, by its irritating and characteristic odour, and, secondly, by reducing alkaline silver nitrate, and thus producing a black deposit (*vide* test for glycerin).

3. When heated in a crucible for a short time with a mixture of potassium hydrate 5 parts, and potassium nitrate 1 part, it is broken up with the formation of potassium phosphate. This may be detected in the residue by dissolving it in a little distilled water, adding 2 c.c of dilute HNO_3, and an equal volume of ammonium molybdate; when boiled, yellow crystals of ammonium phospho-molybdate separate out.

Lecithin may be hydrolysed by boiling it with acids or alkalies. It yields, as a result of such treatment, the following bodies :—

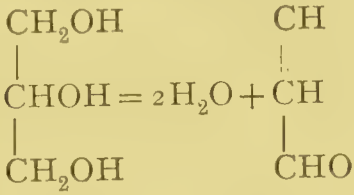
1. Oleic Acid.—An unsaturated fatty acid of the formula $C_{17}H_{33}COOH$, belonging to the acrylic series. The osmic acid reaction, a reduction of the tetroxide of osmium to the lower oxide, depends upon the presence of this unsaturated fatty acid.

2. Stearic Acid, $C_{17}H_{35}COOH$, of the saturated fatty acid series.

3. Glycerin, a triatomic alcohol, of the formula

$$= \left\{\begin{array}{l} CH_2OH \\ \;| \\ CHOH \\ \;| \\ CH_2OH \end{array}\right.$$

This body, on being heated with $KHSO_4$, yields water and acrylic aldehyde or acrolein, in accordance with the equation—



$$\begin{array}{c} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} = 2H_2O + \begin{array}{c} CH \\ \| \\ CH \\ | \\ CHO \end{array}$$

4. PHOSPHORIC ACID (H_3PO_4).—The glycerin and phosphoric acid are usually combined as glycero-phosphoric acid.

5. A nitrogenous base, CHOLINE.

Choline.—This substance is of importance because of its clinical significance. For all practical purposes, it may be stated that normal cerebro-spinal fluid contains no choline. Lecithin is an abundant constituent of nervous tissue, and, when it disintegrates, choline is liberated. In organic disease of the nervous system, such as "general paresis of the insane," choline may be detected in the cerebro-spinal fluid. Halliburton and Mott, in a number of experiments upon cats, have divided the sciatic nerves producing Wallerian degeneration, the result of which is that choline is liberated, and can be detected in the blood of the animal. In functional nervous disease, such as hysteria and some cases of epilepsy, no choline can be detected in the cerebro-spinal fluid. Halliburton and Mott therefore recommend the routine examination of cerebro-spinal fluid for choline as a means of distinguishing between nervous diseases of functional and organic origin.

The most important of the reactions for choline are—

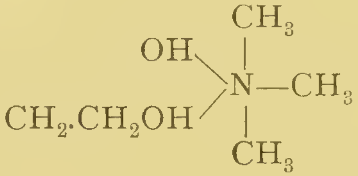
1. The preparation of choline-platino-chloride. This salt is prepared by adding to an alcoholic solution of the residue, left after evaporating a measured volume of choline to dryness, an alcoholic solution of platinum chloride. If this is allowed to stand, crystals of the choline-platino-chloride separate out, which are yellow, octagonal in shape, insoluble in 15 per cent. alcohol, and contain 31 per cent. of platinum.

2. If to these crystals, or to the extract, a small amount of a potassium iodide solution of iodine is added, crystals of a rhombic shape are obtained, which, superficially, have a very marked resemblance to hæmin crystals. They consist of choline periodide. If allowed to stand, they appear as oily droplets, becoming converted to the lower iodide. On the addition of more iodide solution, the periodide is again regenerated.

3. The third test for choline is a biological reaction.

Choline, injected into the circulation of an animal, causes a distinct fall of arterial blood pressure, a fall, however, which is prevented by a previous injection of atropine. The fall in blood pressure is due to an effect upon both the central and peripheral regulatory apparatuses of the blood pressure, causing a dilatation of the arterioles, and a weakening and slight slowing of the heart beat. It has been shown that the acetyl derivative of choline is one million times more active in producing a fall of blood pressure, than adrenaline is in inducing a rise.

Chemically considered, choline is an alkaloid, belonging to a group of compounds, of which other members are **Muscarine**, the poisonous alkaloid of the toad-stool, **Neurine**, an alkaloid derived from nervous tissue, and **Betaine**, the innocuous alkaloid of the beet. It contains carbon, hydrogen, oxygen, and nitrogen, and has the formula $C_5H_{15}NO_2$, or written structurally—



that is, trimethyloxyethylammonium hydroxide.

It is interesting that it contains the group

$$N(CH_3)_3 \text{ or trimethylamine.}$$

The significance of lecithin in the body is unknown; but it has been suggested that, in the case of hæmolysis brought about by the cobra toxin, lecithin plays the part of an amboceptor, linking on the complement, present in cobra poison, to the erythrocytes. Further, arising from this, and, on the ground advocated by Ehrlich, that his side chain theory not only applies to pathological processes such as hæmolysis, bacteriolysis, etc., but actually represents the normal process of food assimilation, it has been suggested that lecithin plays the part of a normal amboceptor in the processes of the assimilation of proteins by the tissue cells. Recent work seems to have shown clearly enough, however, that lecithin itself does not play the important part previously assigned to it, but that, in hæmolysis, the active agent is really lecithin minus oleic acid, or deoleolecithin.

Kephalin.—This substance is more abundant in nervous tissues than lecithin; further, it is not confined to the white substance, or myelin, of nervous tissue, but occurs in even greater quantity in the grey substance, that is in the nerve cells and their processes. It is also present in egg-yolk. Kephalin differs from lecithin in that it is insoluble in alcohol. On hydrolysis, it yields glycerin, phosphoric acid, a base which is possibly choline, and fatty acid less saturated than oleic acid.

Sphingomyelin is a white substance which forms one of the constituents of the so-called protagon of nervous tissue. It occurs in the cortex of the suprarenal capsules. On hydrolysis, it yields an alcohol, an unsaturated fatty acid, and the base choline. It differs from lecithin in that it yields no glycerin on hydrolysis. Sphingomyelin is lævo-rotatory.

Jecorin was first isolated from the liver of the horse, but, more recently, it has been obtained from other organs. It consists of a diamino-monophosphatide, united to sugar, of which it contains about 14 per cent.

ORIGIN OF THE PHOSPHATIDES.

The fact that the phosphatides are found in great abundance in the cortex of the suprarenal capsules has led to the supposition that the cortex of the suprarenal gland may be an organ, the function of which is the production of some of the lipoid bodies.

FUNCTION OF LIPOIDS.

The function of the lipoids in the body is not definitely known, but the following are some of the views which have been advanced:—

1. Bang was the first to point out the importance of the lipoids in the process of life. He showed that while the proteins have been supposed to be the chief agents in biotic or physiological changes, the lipoids are of equal, and, in some cases, of greater chemical lability. He maintains that the lipoids play some part at least as "carriers of life."

2. Since the lipoids occur in the liver, where the fatty acids are desaturated previous to their further oxidation, they have been supposed to play some part in this desaturation process.

3. Since the lipoids are so easily oxidised, they have been supposed to be of some importance in oxidation processes in the body generally.

4. They are important from the standpoint of the action of narcotic drugs, and, indeed, it was in this connection that the term "lipoid" was first introduced. The narcotic drugs are soluble in the lipoids, and it has been suggested that it is, by the solubility of these drugs in the lipoids, which exist in the nerve cells, that the physical conditions in these cells are so altered that narcosis is induced.

CHAPTER VII.

ENZYMES.

It is well known that the living body is able to effect chemical changes, which the chemist has not been able to accomplish without the use of strong reagents and much heat. Such a change may be instanced in the conversion of proteins into amino-acids. In the animal body this change is effected easily and rapidly; outside the body it has only been found possible to accomplish it by the use of strong acids or alkalies and prolonged heating. Again, the body instantly effects syntheses of complex materials, which, as yet, have never been effected in the chemical laboratory. These changes in the body are produced by the activities of different enzymes. For example, it is found that in the secretion of the salivary glands there is a body (ptyalin) which is capable of converting cooked starch into maltose. Moreover, unlike most chemical reactions, this body is quite unchanged in the process. If the action on the starch comes to an end (which occurs when only a minute amount of the original starch is left), the addition of more starch to the reacting mixture causes a still further disappearance of the added starch with the formation of more sugar, and so on *ad infinitum*. Such property is the main characteristic of an enzyme. An enzyme is a body, produced by a living organism, or cell, and is capable of effecting chemical change without itself undergoing alteration in the process.

FERMENTATION.

Before the enzymatic activities of the various secretions of the intestinal tract had been demonstrated, it was known that various living organisms were capable of effecting changes of a similar nature. Thus the yeast cell (by virtue of the enzyme zymase) splits glucose into alcohol and carbon dioxide—

$$C_6H_{12}O_6 = 2C_2H_5OH + 2CO_2,$$

a change which has long been known as "fermentation." Kühne was the first to draw the line of distinction between processes such as these, and those effected by the intestinal secretions. Since Kühne's time, however, many investigations have demonstrated that no such difference exists between the two classes. Büchner, by crushing the yeast cell, was able to show that the juice still had the property of decomposing sugar into alcohol and carbon dioxide. The enzyme was intracellular, and was confined within the limits of the yeast cell. Subsequent research has demonstrated the existence of a great many of these intracellular enzymes in the cells of the mammal, and the most convenient classification of the enzymes of the mammalian body consists in confining them to the limits of—

1. Extracellular enzymes, or exo-enzymes.
2. Intracellular enzymes, or endo-enzymes.

PREPARATION OF THE ENZYMES.

Different methods must be used for the preparation of the extracellular and the intracellular enzymes.

(*a*) **Extracellular Enzymes.**—These enzymes can be most readily prepared by the addition of absolute alcohol to the secretion. This precipitates the protein and the enzymes also, probably in a physical combination with one another. This precipitate can be kept indefinitely without deterioration in the activity of the enzyme. The enzyme can be obtained, whenever required, by simple water extraction of the precipitate, the alcohol having coagulated the protein.

(*b*) **Intracellular Enzymes.**—The preparation of these is more complex, since they are so intimately united with the cell protoplasm. Preparation first involves rupture of this union. The tissue to be investigated, *e.g.* the liver, is thoroughly disintegrated by grinding it up with sand. The liver pulp is then mixed with a mixture of glycerin and water, and allowed to stand for three weeks, during which time it must be frequently shaken. By this means the intracellular enzymes are dissolved out, and on filtration a juice rich in them is obtained. If it is required, they may be precipitated by the addition of absolute alcohol.

CHEMICAL PROPERTIES OF ENZYMES.

Enzymes have never been obtained in sufficient quantities for exact chemical analysis, and, moreover, not one of them appears to have been isolated in an absolutely pure condition. But this can be said, that probably the different enzymes differ in chemical composition, although it is quite uncertain what these differences are. Inorganic catalysts have a definite chemical composition; it may therefore be concluded that organic catalysts, or enzymes, are bodies of definite chemical composition too. Because of their universal occurrence in living material, and because, so far as is known, proteins only are universal in living matter, it has been assumed that the enzymes are protein in nature. Certainly, many so-called pure enzyme preparations give the protein reaction, but this is probably due to the tendency which enzymes have of separating out in mechanical combinations with flocculent precipitates. Enzymes are soluble in water, in glycerin, and in dilute salt solution. They are precipitated by absolute alcohol, acetone, ether, or mixtures of two or even the three of these. It is quite possible, however, that even this precipitation is not a true precipitation of the enzyme itself, but a precipitation of the protein present in the solution which comes down with the enzyme in loose combination.

PHYSICAL PROPERTIES OF ENZYMES.

For the most part enzymes are colloidal in nature. They have the property of carrying down with them the constituents of the solutions from which they are precipitated. This explains why amylase and invertase usually give carbohydrate reactions, and why pepsin and trypsin give protein reactions. Enzymes are remarkably affected by heat; thus a solution of diastase at once loses its property of hydrolysing starch if heated to a temperature of 80° C., yet, if the dry enzyme is heated to a temperature of 100° C. for a considerable time, when dissolved in water again, it exhibits its characteristic activity. This fact stands in correlation with another previously mentioned, that, in the dry state, enzymes will maintain their activity for a considerable time unimpaired, although, in a state of solution, they quickly tend to lose their activity. The best condition for an enzyme action is furnished by a temperature of 40° C. At this temperature the enzyme exhibits a maximum activity, or in other words the "velocity of the action" is greatest at this temperature. There are, however, exceptions to this rule; for instance, malt diastase acts best at 60° C.

ENZYME ACTION.

Within recent years the action of enzymes has been carefully investigated, and, owing at the same time to the great advance made in the science of physical chemistry, the nature of this action has been elucidated. The following appear to be the chief points demonstrated:—

1. The reactions brought about by enzymes are not initiated by that particular enzyme alone. The action of the enzyme appears to consist in a quickening of a particular reaction. Thus it is known that a high temperature will cause the proteins, when in contact with water, to undergo cleavage into their constituent amino-acids. By physico-chemical methods the velocity of this cleavage can be measured. But physical chemistry has demonstrated that if any particular reaction is affected, as regards its velocity, by temperature, then the reaction velocity is doubled by every rise of 10° C.; thus, if a reaction has a rate represented by 2 at 10°, it will become 4 at 20°, 8 at 30°, and so on.

Applying these facts to the action under consideration, it follows that whereas the proteins are hydrolysed by water at ordinary temperatures, but at an exceedingly small velocity, in the presence of an enzyme (*e.g.* when trypsin is added and the conditions are such as enable it to exert its activity), the velocity of this change is enormously accelerated, and a reaction occurs which formerly did not appear to take place, simply because of its small velocity.

2. The reaction does not take place to the complete destruction of the substrate (*i.e.* the body acted upon).

The reactions accelerated by enzymes are all of the nature of equilibrated reactions, a characteristic which depends upon their reversibility. A simple example may be conveniently studied in the case of the hydrolysis of ethyl acetate by acids (*e.g.* hydrochloric acid). Hydrochloric acid splits up ethyl acetate into acetic acid and ethyl alcohol, a reaction which is expressed by the formula—

$$CH_3COOC_2H_5 + H_2O = CH_3COOH + C_2H_5OH$$

At the same time, though perfectly correct in so far as it expresses the change taking place, it indicates too much. It suggests that all of the $CH_3COOC_2H_5$ present in the solution undergoes hydrolysis, but this is not the true state of affairs. No matter how long the reaction is prolonged, the conditions remaining the same, a certain amount of $CH_3COOC_2H_5$ remains in the solution. Starting with molecular proportions of water and $CH_3COOC_2H_5$, the reactions proceed until there are left in the solution $\frac{1}{3}$ molecule of $CH_3COOC_2H_5$, $\frac{1}{3}$ of H_2O, $\frac{2}{3}$ of CH_3COOH, and $\frac{2}{3}$ of C_2H_5OH (Berthelot and P. de St. Gilles).

On the other hand, if C_2H_5OH and CH_3COOH are brought together, the reaction proceeds in the reverse direction, with the formation of $CH_3COOC_2H_5$ and H_2O, according to the equation—

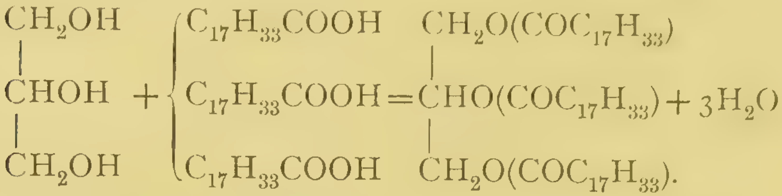
$$C_2H_5OH + CH_3COOH = CH_3COOC_2H_5 + H_2O$$

until in the final products, the same degree of concentration of the reacting products is reached as in the reverse direction. For economy of space, and greater lucidity of expression, it has become the custom to express the two reactions in one equation, thus—

$$CH_3COOH + C_2H_5OH \rightleftarrows CH_3COOC_2H_5 + H_2O$$

Such an expression indicates a reversible reaction, indicating that with these four substances in a given solution, the reaction will proceed either in the one direction or in the other until equilibrium is reached. If, when such equilibrium has been obtained, any one of the reacting bodies (*i.e.* CH_3COOH) is removed, the two reactions will progress unequally until a new condition of equilibrium is obtained. Enzyme actions are simply accelerations of such reactions, and consequently it is easily understood how, under certain given conditions, syntheses are effected instead of decompositions. For example, lipase, an enzyme present extracellularly in the pancreatic juice, and intracellularly in many tissues, such as the liver and the mucous membrane of the intestine, hydrolyses fats into glycerin and fatty acids, and is, in all probability, able to bring about the synthetic production of the fats from their constituents.

Recently it has been shown that the fat triolein, a normal constituent of the fats of the body, can be synthesised from oleic acid and glycerin, thus—



$$\begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} + \left\{ \begin{array}{l} C_{17}H_{33}COOH \\ \\ C_{17}H_{33}COOH \\ \\ C_{17}H_{33}COOH \end{array} \right. = \begin{array}{l} CH_2O(COC_{17}H_{33}) \\ | \\ CHO(COC_{17}H_{33}) + 3H_2O \\ | \\ CH_2O(COC_{17}H_{33}). \end{array}$$

Lœvenhart has pointed out the physiological importance of this reversibility of lipase-action. During digestion, fat taken as food is hydrolysed in the lumen of the intestine into glycerin and fatty acid, but, during the absorption of the products of fat digestion, fat globules are found in the columnar cells over the villi. There must obviously be some particular mechanism by which the products of fat hydrolysis are resynthesised in the columnar cells after absorption. If lipase is present in these cells, it certainly would be capable of synthetic action. Lœvenhart has obtained a lipase from the mucous membrane of the intestine of a pig after completely washing away the pancreatic enzymes. A similar enzyme has been obtained from the liver and other tissues where the storage of fat occurs. "In all these cases, when the blood and lymph bathing the cells become poor in fatty acid and glycerin, owing either to fat being stored elsewhere or to its being used up by oxidation, as in starvation, the lipase restores equilibrium by effecting hydrolysis of the fat which had been previously stored up" (Bayliss).

The enzyme maltase hydrolyses maltose into dextrose. Croft Hill has shown that, if maltase is allowed to act upon a strong solution of glucose, a synthetic process occurs and maltose is formed. In the original experiment some isomaltose ("revertose") was produced, but this is explained by Bayliss as being due to the action of emulsin, another enzyme contained in yeast. It is, therefore, concluded by Bayliss that there is no cogent evidence that enzymes produce by synthesis any bodies different from those which they hydrolyse.

Little is known about the possible synthetic action of the proteolytic or proteoclastic enzymes. It has been found that a protamine may be synthesised by trypsin from its cleavage products. Leathes has pointed out that the facts as to the synthesis of protein in the body distinctly indicate a reversible enzyme action. Animals are able to maintain their nitrogen-content on a diet in which the only nitrogenous bodies are the products of the prolonged action of trypsin and erepsin. The products of protein hydrolysis by acids are, however, unable to take their place.

From these considerations it is quite obvious that both synthesis and hydrolysis, produced by the action of enzymes, are really accelerations of the two different reactions which occur in a "reaction of equilibration," and that whichever of these reactions takes place is determined merely by the conditions present.

THE SPECIFIC CHARACTER OF ENZYME ACTIVITY.

Every individual enzyme is remarkably limited in the scope of its activity. It is able to produce one change, and that change only in one given substance, or a very closely related substance; trypsin will hydrolyse proteins, but it is entirely without action upon the fats; lipase will split the fats, but has no action upon the proteins or the carbohydrates. Then again the bacillus acidi lactici, by means of its intracellular enzymes, will convert glucose into lactic acid,

$$C_6H_{12}O_6 = 2C_3H_6O_3,$$

and the butyric acid bacilli will similarly convert glucose into butyric acid,

$$C_6H_{12}O_6 = C_4H_8O_2 + 2CO_2 + 2H_2:$$

but in no circumstances will the butyric acid bacilli convert glucose into lactic acid, or *vice versa*. In order to explain such specificity, Fischer has formulated his well-known "lock and key theory," according to which every enzyme fits on to its substrate just as a key fits a lock.

NATURE OF ENZYME ACTION.

The nature of enzyme action has always presented great difficulties, and has never been satisfactorily explained. Perhaps the best results will be obtained by a consideration of the characteristics of "catalytic" actions. It is well known that in the inorganic world there are catalytic agents which, like the enzymes, are capable of accelerating particular reactions. Thus, platinum black (or, better still, palladium) is able to cause hydrogen and oxygen to unite, with the result that water is formed in indefinite amounts; colloidal platinum (platinum in a very fine suspension) is able to exert quite an appreciable influence, when present in very minute amounts, upon the decomposition of hydrogen peroxide. Indeed, the analogy is so great that Oswald has suggested that enzymes are no more than *organic catalysers.* If these catalytic actions are examined, it will be seen that the catalytic agent may act in different ways, thus—

1. It may act simply by surface condensation of the reacting bodies, or by absorption. Thus, in the action of platinum black, it is assumed that the gases condense on the very large surface afforded by the fine particles, and that reaction takes place.

2. It may act by the formation of intermediate compounds.

Enzyme action appears to be chiefly due to the former of these conditions, but it is very probable that the formation of intermediate compounds plays a considerable share in its activity.

It is possible, then, that enzymes act as organic catalysts, just as sulphuric acid acts as an inorganic catalyst; the acid, however, requires a high temperature in order to hasten the velocity of its reaction, whereas the optimum temperature for the organic catalysts is 40° C.

It is assumed, therefore, that enzymes are catalysts produced by living organisms.

THE "VELOCITY OF REACTION."—By this term is meant the time which is occupied by an enzyme in bringing about a given change in a fixed amount of material or substrate. In general terms it is found that the amount of enzyme, multiplied by the time of reaction, equals a constant, or in other words, that the velocity of reaction is proportional to the amount of enzyme present. For rennin, this velocity of reaction may be ascertained by observing how long it takes a given amount of the enzyme to coagulate a definite amount of milk.

THE ACHROMIC POINT.—The determination of the achromic point may be brought about in the following way: 5 c.c. of a 5 per cent. solution of starch are mixed with a given quantity of filtered saliva, and placed in a water bath at 40° C., in order that the ptyalin may convert the starch into soluble starch, erythro-dextrin, achroö-dextrin, and finally maltose. A drop of this digesting mixture is tested every half-minute with a fresh drop of iodine solution. At first a blue colour is produced, then a violet (indicating the presence of starch and erythro-dextrin), then a red (due to erythro-dextrin), finally no distinct colour occurs; this is the achromic point and means that the maltose stage is reached. The velocity of reaction is determined by measuring the time that it takes for the achromic point to be obtained.

The proteolytic or proteoclastic activity of digestive juices may be determined by one of the following methods:—

ROAF'S METHOD—*for pepsin.*—Two equal weighed quantities of fibrin, previously stained with congo-red solution, are placed in two test tubes with an equal quantity of the two gastric juices to be compared. These are allowed to digest for fifteen minutes. The fibrin is digested and the colouring matter set free; the congo-red comes out into the solution and is turned blue by the acid present. A few crystals of sodium carbonate are added and the solution is turned red. The redder fluid is diluted in water until it is the same tint as the less red fluid. The amount of dilution necessary will measure the relative activity of the two gastric juices. *For trypsin*, the same method of procedure obtains, but the congo-red comes out into the solution and remains red.

METHOD WITH METT'S TUBES.—Small pieces of capillary glass tubing of definite length are filled with egg-white and heated to 95° C. to coagulate the albumin. These tubes are placed in the digestive fluid (gastric or pancreatic) for a given time, after which they are taken out, and, if the digestion has not gone too far, only a portion of the protein will be digested, which amount can be measured. The tubes may be previously filled with gelatin, and the digestive action of pepsin and trypsin ascertained at room temperature, for, at body temperature, the gelatin melts. The tubes may be filled with starch paste and the amylolytic activity of ptyalin and amylopsin determined.

The nature of the combination between the enzymes and the substrate—

In order that an enzyme may exert its activity, it is believed that a preliminary combination of some kind or other between the enzyme and the substrate is necessary. It has been stated that enzymes are of the nature of colloids, and these are particularly prone to form *adsorption-compounds*. It is quite possible, therefore, that, in the early stage of enzyme action, an adsorption-compound is formed between the enzyme and the substrate, and that after this close association has taken place, the proper chemical actions, due to the agency of the enzyme, begin to make their appearance.

CLASSIFICATION OF ENZYMES.

Enzymes are classified partly according to their action and partly according to the particular substrate or substance upon which they act.

1. *Amylolytic Enzymes.*—By a hydrolytic cleavage of the starch molecule, these convert the polysaccharides into dextrins, and finally into maltose.

Diastase of vegetable seeds converts starch into maltose.

Ptyalin of saliva converts cooked starch into maltose.

Amylopsin of pancreatic juice converts cooked and uncooked starch into maltose.

The change however may not always be in the direction of the formation of carbohydrates of lower molecular weight, because in the intestine there are bacteria which, by virtue of an enzyme (presumably), convert cellulose $(C_6H_{10}O_5)_n$ into carbon dioxide and marsh gas, thus—

$$(C_6H_{10}O_5)_n + (H_2O)_n = 3(CO_2)_n + 3(CH_4)_n.$$

2. *Inverting Enzymes.*—These convert the disaccharides into monosaccharides.

Invertase of yeast cells converts cane sugar into dextrose and lævulose.

Invertase of succus entericus converts cane sugar into dextrose and lævulose.

Maltase of succus entericus converts maltose into dextrose.

Lactase of succus entericus converts lactose into dextrose and galactose.

3. *Lipolytic Enzymes.*—These split neutral fats into glycerin and fatty acid.

Gastric lipase splits small quantities of emulsified fat into glycerin and fatty acid.

Pancreatic lipase splits emulsified fat into glycerin and fatty acid.

Lipolytic enzymes also split the phosphatide, lecithin, into glycero-phosphoric acid, fatty acids, and choline.

4. *Proteolytic or Proteoclastic Enzymes.*—These by a process of hydrolysis split proteins into proteoses, peptones, etc.

Pepsin of the gastric juice splits proteins into proteoses and peptone.

Trypsin of the pancreatic juice splits proteins into proteoses, peptones, polypeptides, and amino acids.

5. *Peptolytic Enzymes.*—These split proteoses and peptones into polypeptides and amino-acids.

Erepsin of the succus entericus splits proteoses and peptones into polypeptides and amino-acids, and, in a similar way, it splits caseinogen.

6. *Coagulative Enzymes.*—These convert soluble into insoluble proteins.

Thrombin (fibrin-enzyme or thrombase) converts fibrinogen into fibrin.

Rennin or rennet converts calcium caseinogenate into insoluble casein.

There is probably a coagulative enzyme which converts paramyosinogen and myosinogen into insoluble myosin during rigor mortis.

7. *Autolytic or Intracellular Enzymes.*—These enzymes are all important in the metabolic, or intracellular, chemical changes which take place in the protoplasm of the cells and tissues. They are divided into amylolytic, lipolytic, proteolytic, and peptolytic, according to the kind of substrate upon which they act. After death of the tissue their activity may continue so that they may cause self-digestion or *autolysis* of the cells and tissues in which they are situated, so long as the organ in which they exist is kept at a suitable temperature and under strict aseptic conditions. In certain tissues nuclease exists, which causes nucleic acid to liberate the two purine bases, adenine ($C_5H_3N_4NH_2$) and guanine ($C_5H_3N_4O.NH_2$). Autolysis proceeds much more rapidly in fasting tissues than in well-fed tissues, and in starvation, in all probability, these autolytic enzymes are at work.

8. *Oxidases, or Oxidising Enzymes.*—These are intracellular enzymes, which carry oxygen and produce oxidation. They are all important in internal or tissue respiration and in metabolism; thus oxidase brings about the conversion of hypoxanthine ($C_5H_4N_4O$) into xanthine ($C_5H_4N_4O_2$) and xanthine into uric acid ($C_5H_4N_4O_3$). These oxidases are most abundant in the liver and spleen.

9. *Deamidising Enzymes.*—These split off the NH_2 group from certain nitrogenous compounds, thus—

Adenase splits off NH_2 from adenine ($C_5H_3N_4.NH_2$), forming hypoxanthine ($C_5H_4N_4O$).

Guanase splits off NH_2 from guanine ($C_5H_3N_4O.NH_2$), forming xanthine ($C_5H_4N_4O_2$).

There are also certain intracellular enzymes which are capable of splitting off NH_2 from amino-acids.

10. *Urea-producing Enzymes.*—These by a process of hydrolysis, or some more complicated reaction, produce urea.

Arginase causes the production of urea and ornithine from arginine.

The uricolytic enzyme causes the production of urea from uric acid; this enzyme is produced in the tissues, and especially in the liver.

CO-ENZYMES.

Some enzymes are secreted in the active condition, and are able to act straight away without the intervention of any other substance, provided that the reaction of the medium is such as is suitable for their activity. But this is not the case with all of them. Trypsin is not secreted as such in the pancreatic juice, but as a zymogen, trypsinogen, which has no action whatever upon proteins. It requires the presence of an activator, or co-enzyme before it becomes the active trypsin. The activator is enterokinase, a substance produced by the glands of the intestinal mucous membrane. How the enterokinase acts upon the trypsin is an open question. Recent experiments of Delezenne show that inactive pancreatic juice may be activated by calcium salts as well as by enterokinase. The amount of calcium in the juice as secreted is sufficient to bring about very slow activation, but the process can be considerably accelerated by adding more calcium (Bayliss).

Enzymes, being colloids, are sensitive to the action of electrolytes. In some cases they appear to be inactive without the presence of one or other of these agents. In these cases, therefore, the electrolyte appears to play the part of a co-enzyme. Hydrochloric acid similarly appears to be a necessary co-enzyme in the formation of pepsin from pepsinogen. Thrombogen is activated by thrombo-kinase in the presence of soluble calcium salts to form thrombin or fibrin enzyme. Pancreatic lipase requires the presence of bile salts for its activity, and zymase, the enzyme of yeast which causes alcoholic fermentation, requires the presence of phosphates.

ANTI-ENZYMES.

If enzymes are injected into the blood, they give rise to toxic effects, but, if the successive injections of small quantity are made, bodies are produced which nullify the effect of the injected enzyme. Such anti-enzymes have been produced by the injection of enzymes. Similar anti-enzymes occur normally, however, and have been found by Weinland in the intestinal tract. In the stomach mucous membrane, there occurs an anti-body, *anti-pepsin*, which protects the mucous membrane from the action of the gastric juice, and similarly *anti-trypsin* is secreted by the mucous membrane of the intestine. Such bodies are of great economic importance, since they protect the various subdivisions of the alimentary canal from auto-digestion by its own enzymes. Recent work by Hamill and by Bayliss has thrown considerable doubt about the presence of anti-trypsin in the intestinal mucous membrane. According to the observation of Klug, the actual body, which has the power of protecting the cells of the mucous membrane, is the *mucin* which is always present in considerable quantities. This protection is brought about by the formation of adsorption-compounds with the enzymes. Weinland made another interesting observation, that the presence of anti-trypsin, in a parasitic worm infecting the alimentary canal, resists the digestive action of the pancreatic juice. The liver cells pour into the blood stream an anti-enzyme, *anti-thrombin*, which neutralises the action of the fibrin-enzyme, which is continuously produced in small quantities. In this way circulating blood is prevented from clotting (*vide* p. 125).

ZYMOGENS.

Extracellular enzymes are derived from the cells, where they have previously existed, not as enzymes, but as zymogen granules, which at the moment of extrusion from the cells appear to become transformed into enzymes. In certain cases, however, the zymogen is extruded as such without change; thus trypsinogen leaves the pancreatic cells as the inactive trypsinogen. Pepsinogen likewise appears to be extruded from the cells of the gastric glands as such, and to be activated by hydrochloric acid, and converted into pepsin. Further, it appears that pepsinogen is less susceptible to alkalies than pepsin, which is rapidly destroyed by them. Although the zymogen may be readily converted into the active enzyme, the reverse process can be brought about. The zymogen of thrombin is prothrombin or thrombogen, which is shed out of the blood platelets and the leucocytes.

AUTOLYSIS.

If an organ, such, for example, as the liver or kidney, is thoroughly minced, and kept in chloroform water or water containing thymol, it is found to undergo a process called "autolysis" or "auto-digestion." That is to say, a quantity of the protein, fat, and carbohydrate contained in the organ passes into solution, and, at the same time, a considerable amount of ammonia is evolved. Such change occurs most quickly, if the organ is kept at the body temperature, and is due to the action of the endo-enzymes. These are set free from their anchorage in the protoplasm of the tissues in the process of mincing, and become subsequently dissolved in the water, so as to exert their action upon the chemical constituents of the organ. These enzymes, which are proteoclastic, nucleoclastic, amyloclastic, and lipoclastic, are present in the various organs of the body.

The proteins are disintegrated into simpler bodies by a variety of enzymes. Thus, proteoses are converted by them into peptone, and the nucleo-proteins into peptone and nuclein. The peptone is then subjected to the action of endo-erepsin and split up into amino-acids, which are still further broken up, with the formation of ammonia. Nuclein is split up by nuclease, and its purine content is further attacked by the purinases, oxidases, and uricolytic enzymes: the result of the action of which is the formation of uric acid and urea. Similarly arginine is split by arginase into urea and ornithine.

Fats similarly are split up into fatty acid and glycerin by the action of the liberated endocellular lipase.

Carbohydrates are split up by the action of diastases.

These split up the glycogen, present in the organs, with the formation of maltose which is further hydrolysed into glucose by the maltase present. In normal circumstances, the autolytic enzymes, present in the various tissues, are inhibited in their activity by the plasma which bathes the tissues.

OXIDATION-PROCESSES.

So far the enzymes, dealt with in the preceding pages, have all exerted their action by a process of hydrolysis. There are, however, various enzymes concerned in the mechanism of oxidation. According to Bach and Chodet, there are three distinct sets of bodies which are capable of bringing about oxidation-processes.

1. Organic peroxides, including hydrogen peroxide.
2. Peroxydases.
3. Catalases.

Of these the peroxydases and catalases are of enzyme nature. They are both capable of decomposing hydrogen peroxide with the formation of the water and oxygen; peroxydase appears to separate oxygen in the active state (atomic oxygen), catalase separates oxygen in a relatively inactive state (molecular oxygen). Peroxydase acts upon various organic peroxides and hydrogen peroxide, whereas catalase acts upon hydrogen peroxide only. It is possible that hydrogen peroxide may be produced as a by-product of oxidation in the animal tissues; if so, it is necessary that it should be forthwith destroyed, owing to its toxic action on protoplasm (Bayliss). It is quite possible, therefore, that the catalase, which appears to be widespread in the organism, brings about the destruction of the hydrogen peroxide.

A peroxydase alone, without the presence of a peroxide, is of no use as an oxidising agent, so that the system of peroxide and peroxydase forms the active combination. This system is known as an *oxydase*.

SECTION III.

DIET AND DIGESTION.

CHAPTER VIII.

DIET.

THE proximate principles of life consist of the following :—

1. Proteins.
2. Fats.
3. Carbohydrates.
4. Salts.
5. Water.
6. Oxygen.

In order that the cells and tissues of the body may carry out their physiological functions, they must be supplied with these substances in proper proportions. According to Halliburton, a healthy and suitable diet must possess the following characters :—

1. It must contain the proper amount and proportion of the various proximate principles.

2. It must be adapted to the age of the individual, to the amount of work done by him, and to the climate in which he lives.

3. The food must contain, not only the necessary amount of the proximate principles, but these must also be present in a digestible form.

It is found that a healthy man doing a fair day's work, on an ordinary diet, eliminates from 250 to 280 grms. of carbon *per diem*, which escape chiefly from the lungs as carbon dioxide. He also eliminates *per diem* from 15 to 18 grms. of nitrogen. This is present in the urine as urea, uric acid, and creatinine. These substances, CO_2, creatinine, uric acid, urea (little), are derived chiefly as the result of katabolism, and partly from the food, *i.e.* urea (more).

During the production of these substances, heat is evolved, energy produced, and work done. It has been found that muscular work greatly increases the output of CO_2, and very slightly increases the output of N. In order that metabolism may be kept in equilibrium, anabolism, constructive metabolism, or assimilation must occur, and it is for this purpose that food is taken into the alimentary canal, digested, and absorbed. It may be said that the nutritive value of a diet chiefly depends upon the amount of C and N present in a readily digestible form. The source of the carbon for the body is chiefly carbohydrate, but it is also derived from fat and protein; the source of the nitrogen is the proteins. The following general proportions of the elements in the proteins, fats, and carbohydrates should be noted:—

Protein . . . C_{54}, H_7, O_{21}, N_{16}, S_1 (C 1 in 2).
Fat . . . . C_{48}, H_{98}, O_6 (C 1 in 3) (high heat value).
Carbohydrate . . C_6, H_{12}, O_6 (C 1 in 4) (lower heat value).

Ranke's average adult diet *per diem* is as follows:—

Protein	100 grms.
Fat	100 ,,
Carbohydrate	250 ,,
Salts	25 ,,
Water	2600 ,,

Diet of an infant aged six months, weight 6·7 kilos. (Cautley)—

Protein	20 grms.
Fat	40 ,,
Carbohydrate	70 ,,
Salts	2 ,,
Water	868 ,,

Voit arrived at the fact that 118 grms. of protein are required for an adult *per diem.* On the other hand, Chittenden fixes 60 grms. *per diem* as the best amount of protein for habitual consumption, and an intake above this he regards as a *luxus consumption.* It is generally believed, however, that a large amount of foreign protein must be digested for the appropriate simple amino acids and aromatic amino acids to be set free, in order that they may be assimilated and built into the native proteins of the body, which, as the result of wear and tear, are being slowly disintegrated. The excess of the amino-acids is split into two portions—a nitrogenous part, which is converted into urea in the liver, and a non-nitrogenous part, which is utilised much in the same way as carbohydrates and fats are, that is, to be finally oxidised to form CO_2 and H_2O, with the evolution of heat and energy.

According to Hutchison, an infant of six months, weighing 6·7 kilos., and taking an average quantity of breast milk (950 grms.), consumes about 14 grms. of protein *per diem.* This is about 2 grms. of protein per kilo., so that, if an adult of average weight (70 kilos.) consumed the same proportion of protein, he would require 140 grms. in his diet, which is considerably above Voit's standard. The child, however, is growing, *i.e.* continually forming new cells, of which the chief constituent is protein. It is obvious, therefore, that, in proportion, a growing child requires more protein than the full-grown adult. On the other hand, it may be pointed out that the adult, in proportion, performs more muscular work than the child, and this muscular work causes a small amount only of wear and tear of the tissue proteins. If it is desired to cause the tissues of the adult to hypertrophy, as occurs in the muscles when an individual goes into training, in order that there may be a storage of protein in the body, there must be an increased protein intake, and at the same time, the muscles *must* be exercised. For a healthy adult, it is doubtful whether the minimum protein diet is the optimum diet. It is true that a persistent *luxus consumption* of protein tends to produce disease, but it is equally true that those whose protein consumption is above the minimum are better able to resist disease. During pregnancy, too, it is essential that the protein intake should be well above the minimum in order to provide for the hypertrophy of the uterus and the mammæ, and the development of the fœtus and placenta. For a somewhat similar reason, the protein intake should be the optimum during lactation.

It must, therefore, be remembered that an adult requires *per diem* about 100 grms. of fat, whereas an infant weighing 6·7 kilos. obtains through its milk food nearly 40 grms. of fat *per diem.* Fats have a high heat value, because of the proportionately large amount of C which they contain, and infants require such food in order to maintain their temperature, which the healthy adult maintains, to a very considerable extent, by exercise.

The following dietary (after G. N. Stewart) may be taken as typical of what a healthy adult male, doing a fair amount of work, will usually consume *per diem* :—

Lean meat	250 grms.	(9 oz.).
Bread	500 ,,	(18 oz.).
Milk	500 ,,	($\frac{3}{4}$ pint).
Butter	30 ,,	(1 oz.).
Fat (with meat)	30 ,,	(1 oz.).
Potatoes	450 ,,	(16 oz.).
Oatmeal	75 ,,	(3 oz.).

MILK.

For an infant, human milk is a perfect food. It contains all the proximate principles in suitable proportions, and enough iron to meet the requirements of the growing infant, since the liver of the infant has already stored iron from the placenta for use during the first six months of its existence. For an older child and a healthy adult, inconveniently large quantities of milk would have to be taken in order that the right amount of solids might be acquired, and moreover it contains insufficient iron for them. Milk quickly satisfies the feeling of hunger, because it does not stimulate the gastric mucous membrane to increased secretion, *i.e.* it produces no "appetite juice," and the fat or cream of milk actually delays the secretion of gastric juice. The proteins of milk require less pepsin to digest them than do the proteins of meat.

The Mammary Gland.—This gland is made up of lobes, each of which consists of lobules. The lobules consist of acini, opening into the ductules, which open into the lactiferous ducts, and these, in their turn, open on to the nipple. Near the end of each lactiferous duct, there is an ampulla where the milk is temporarily stored. Each acinus is lined by cubical or secreting cells. Outside the acinar walls are the periacinar lymphatics, which are supplied by the neighbouring capillaries. The structure of the acinus depends to a considerable extent upon its physiological state. The young mammary acinus, which has not secreted, is lined with short columnar cells, and the centre is filled by small polyhedral cells; there is a very little fluid present. The acinus, during activity, is lined by somewhat elongated cubical cells, which encroach upon the lumen. The part of the cell adjacent to the lumen seems abnormally large, and contains many kinds of granules, some of which are small, and are stained brown by a solution of osmic acid (1 per cent.): others are larger and are blackened by osmic acid. The smaller granules are probably protein in nature, while the larger ones are fat. These granules are the result of the increased activity of the protoplasm of the cells, which in their turn are supplied by more tissue fluid or lymph, and, at this period, there is also an increased arterial blood supply. The lumen of the acinus is wide and contains a milky fluid rich in fat granules. During

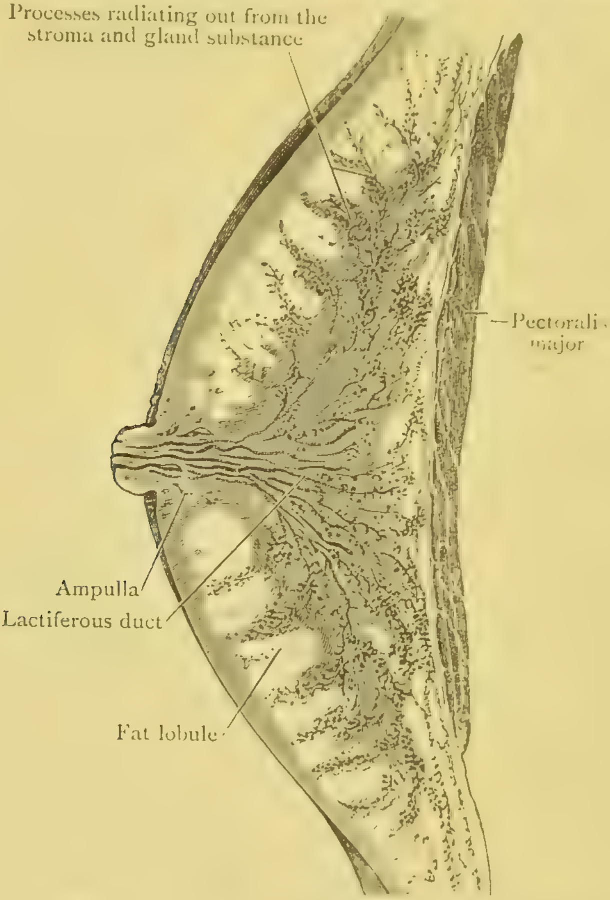


FIG. 6.—Diagram of a section through a Mammary Gland. (Cunningham.)

the later months of pregnancy, the breasts rapidly develop, and prepare for the increased amount of work, which they will be called upon to perform. It is believed by some physiologists that these breast changes are started by a hormone (internal secretion), which is produced by the developing fœtus in utero. During rest the acinus is lined by cubical cells, the nucleus of which is near the centre of the cell, and there are a few fine granules present. The lumen is well defined and contains a fairly clear fluid.

Lactation.—Milk is a secretion produced by the physiological activity of the cells lining the acini of the mammary gland. By the lymph or tissue fluid, the acinar cells are supplied with water, protein (serum globulin and serum albumin), fat (probably in a soluble and invisible form, adsorbed to the proteins of the lymph), carbohydrate (dextrose), and salts. From these substances the acinar cells actively produce the constituents of the milk. Cows fed on grass, *i.e.* water, carbohydrate, and very little protein, yield a milk rich in protein and fat. The composition of milk can, however, to some extent be influenced by the nature of the food. The secretion of milk is, to a certain extent, controlled by the nervous system. At the same time, there is, in all probability, a chemical stimulant or hormone produced by the fœtus, which, during pregnancy, influences the secretion of the mammary gland.

The mammary secretion may be influenced by drugs called galactogogues, such as pilocarpine, which increases the milk flow, whereas anti-galactogogues, such as belladonna, by paralysing the secretory nerves, stop the secretion of milk by the acinar cells.

The milk which is secreted during the first three days, at the commencement of each period of lactation, is called colostrum; it is scanty in amount, and has a slight laxative effect on the child. Its chief characteristics are, that it contains *colostrum corpuscles*, which consist of (*a*) leucocytes, which have wandered into the acini from the neighbouring lymphatics, and of (*b*) cubical cells, which have come away from the acini, and that colostrum also contains a *cell-globulin*, which coagulates on being heated. There is also a smaller amount of calcium caseinogenate than exists in ordinary milk, but more lactalbumin.

COMPOSITION OF MILK.

	Human Milk.	Cow's Milk.	Goat's Milk.
Water . .	87	85·7	86·5
Solids . .	13	14·3	13·5
Protein . .	2 {Calcium caseinogenate, 0·6. Lactalbumin, 1·4.	5 {Chiefly calcium caseinogenate.	4
Fat . .	3·5–4·0	4–4·5	4
Carbohydrate	6·5	4	4
Salts . .	0·25	0·5	0·6

Reaction.—Fresh milk is amphoteric to litmus; this is due to acid and alkaline salts, of which the latter are usually in excess.

Specific Gravity.—That of cow's milk varies from 1028 to 1034. After the lightest constituent (fat) has been removed (skimmed milk), the specific gravity varies from 1033 to 1037.

Proteins.—There are two proteins in milk, caseinogen and lactalbumin. In cow's milk there is twice as much caseinogen as lactalbumin, whereas in human milk there is relatively more lactalbumin. Caseinogen is a phospho-protein, consisting of C.H.O.N.S.P. It has acid properties, is insoluble in distilled water, but forms a colloidal solution in dilute salt solutions. On gastric digestion, it is split into protein and phosphoric acid. It yields no purine bases, and contains no carbohydrate radical. In milk, caseinogen exists combined with calcium as soluble calcium caseinogenate. When acetic acid is added to milk, the calcium unites with the acetic acid forming calcium acetate, and the caseinogen becomes precipitated. When milk becomes sour, lactic acid is produced. This combines with the calcium to form calcium lactate, and caseinogen is precipitated. Like globulin, calcium caseinogenate may be precipitated by full saturation with $MgSO_4$ crystals, with Na_2SO_4 crystals, or half-saturation with ammonium sulphate solution. It differs from globulin, however, in not being coagulated by heat.

If a weak solution of potassium oxalate is added to milk, the following reaction takes place:—

Calcium caseinogenate + potassium oxalate = calcium oxalate + potassium caseinogenate.

In a similar manner sodium and ammonium caseinogenate may be obtained. If calcium chloride is added to oxalated milk, the following reaction takes place:—

Potassium caseinogenate + calcium chloride = potassium chloride + calcium caseinogenate.

Potassium, sodium, and ammonium caseinogenate form a nearly clear solution in water, they do not react with rennin.

Coagulation of Milk.—When milk enters the stomach, the soluble calcium caseinogenate is soon converted into insoluble casein. This change is due to the action of the enzyme rennin in the presence of soluble calcium salts. The coagulation of the calcium caseinogenate appears to occur in two stages. At first the rennin splits the soluble caseinogenate into soluble casein and a soluble protein called *whey-protein.* Soluble calcium salts (*i.e.* calcium chloride, or calcium phosphate) now interact with the soluble casein, producing insoluble casein, caseate of lime, or the chief part of the curd of milk. As a rule, a quantity of fat becomes entangled in the insoluble casein. If milk is previously mixed with an 0·2 per cent. solution of potassium oxalate, it becomes decalcified, that is, the potassium oxalate combines with the inorganic calcium salts present, forming an insoluble precipitate of calcium oxalate. If a little rennin is then added to some decalcified milk in a test-tube, which is placed in a warm bath at 40° C., no clotting of the milk occurs. If, however, a few drops of a solution of calcium chloride are added, and the solution is again warmed to 40° C., coagulation takes place.

The fluid part of milk, left after coagulation has taken place, is called *whey.* It consists of water, lactalbumin, whey-protein, lactose, inorganic salts, some rennin, and a little fat (that which has not been entangled with the casein).

Fats of Milk.—These are the neutral fats, namely, triolein, tripalmitin, tristearin, with a small amount of butyrin, caproin, and caprylin. The most abundant is triolein. These fats are present as a very fine emulsion, and each fat globule seems to be surrounded by a fine envelope of protein, probably calcium caseinogenate.

Tests for the Fats of Milk.—(*a*) Examine milk with the microscope; the fat globules may be readily seen. If a drop of 1 per cent. solution of osmic acid is added, the globules become at first brown, and then black (due to the reduction of the osmic acid by the unsaturated triolein).

(*b*) The osmic acid test may be performed by adding the acid to milk in a test-tube.

(*c*) The fat may be extracted with ether, and if the solution of fat, so obtained, is poured on to filter paper, the ether will evaporate, and a fatty stain be left.

(*d*) The fats may be split into glycerin and fatty acid, and the fatty acid can be detected by the following process: A little fresh milk is boiled in order to kill any micro-organisms and enzymes which may be present. A few drops of a strong alcoholic solution of lacmoid are then added to produce a blue colour. A lipolytic enzyme (pancreatic lipase) is then added, and the mixture kept warm at 40° C. Gradually the blue colour is turned red by the fatty acid which has been liberated from the neutral fat by the lipase.

Milk contains small quantities of the two lipoids, lecithin and cholesterin, and a yellow fatty pigment called lipochrome.

Carbohydrate of Milk.—Lactose is a disaccharide ($C_{12}H_{22}O_{11}$). It is a reducing sugar, and gives the various reducing sugar tests, but, before these are applied to milk, the calcium caseinogenate and fat should be first removed. This is readily done by adding to milk a little 25 per cent. solution of acetic acid; the caseinogen is precipitated and entangles the fat. This may be filtered off, and the filtrate tested for the sugar and lactalbumin by appropriate tests.

The souring of milk is due to the conversion of lactose into lactic acid by the action of certain micro-organisms, and, as lactic acid is produced, it combines with the calcium of the calcium caseinogenate to form calcium lactate, and caseinogen becomes precipitated.

$$\underset{\text{(Lactose)}}{C_{12}H_{22}O_{11}} + H_2O = \underset{\text{(Lactic acid)}}{4(CH_3.CH.OH.COOH)}$$

$$\underset{\text{(Lactic acid)}}{4(CH_3.CH.OH.COOH)} = \underset{\text{(Butyric acid)}}{2(C_3H_7.COOH)} + 4CO_2 + 4H_2$$

Alcoholic Fermentation in Milk.—There are certain fungi which cause the formation of alcohol from lactose, as follows:

$$\underset{\text{(Lactose)}}{C_{12}H_{22}O_{11}} + H_2O = \underset{\text{(Dextrose)}}{C_6H_{12}O_6} + \underset{\text{(Galactose)}}{C_6H_{12}O_6}$$

$$\underset{\text{(Glucose)}}{C_6H_{12}O_6} = \underset{\text{(Alcohol)}}{2C_2H_5.OH} + 2CO_2$$

In this way koumiss is made from mare's or ass's milk; it contains from 1 to 3 per cent. of alcohol.

Salts of Milk.—The most abundant is calcium phosphate, present in order to aid the bone and tooth formation in the young animal. It may be that this soluble calcium salt is one of the factors producing venous thrombosis in patients convalescing from a long illness during which their chief diet has been milk. There are also present potassium chloride, sodium chloride, alkaline sodium phosphate, and a trace of iron combined with protein. The earthy phosphate may be detected in the filtrate, obtained after filtering off the precipitate produced by adding acetic acid to milk, by adding a solution of ammonia; the earthy phosphate is precipitated.

Artificial Feeding of Infants.—There is no doubt that mother's milk is practically a perfect food for the child, but, in some circumstances, it becomes necessary to substitute cow's for human milk. If the compositions of human and cow's milk are compared, it will be seen that cow's milk contains more than twice as much protein per cent. as human milk does, and the protein present is calcium caseinogenate, which forms large and heavy curds with rennin. It is these curds which irritate the infant's stomach and cause dyspepsia and puking. Cow's milk contains rather more fat than human milk, but it contains only two-thirds the amount of lactose. It is richer in calcium salts, but is said to contain less citrates than are present in human milk. When cow's milk is substituted for human milk, it has to be modified to suit the requirements of the infant, and these requirements vary with the age of the child. Water must be added to the cow's milk in order to dilute the proteins present, but in doing this the fats and sugar are unduly diluted. In order, therefore, to raise their percentage in the food for the infant, cream and lactose must be added. A little lime water, too, should be added, for this helps to diminish the size of the curds formed.

For a healthy child of from six to eight weeks old, the following proportions may be used:—

Cow's milk	$\frac{1}{3}$ pint.
Water	$\frac{2}{3}$,,
Cream (obtained by the centrifuge)	4 drms.
Lactose	6 ,,
A little lime water.	

The milk should be pasteurised, that is, heated at 75° C. for at least half an hour and then *rapidly* cooled; the effect of this is to kill any bacilli which may be present, though it does not affect their spores. It is said that milk, treated in this way, loses its anti-scorbutic properties, but this effect may be overcome by allowing the infant from time to time a little orange juice which supplies the necessary citrates.

EGGS.

The shell of eggs consists chiefly of calcium carbonate. Inside the shell is a double shell membrane which encloses the egg, which consists of two parts, the *white* and the *yolk*.

The white of egg is composed as follows:—

Water	86·7 per cent.
Solids	13·3 „
Proteins: egg-albumin egg-globulin ovo-mucoid	12·2 „
Fats and lipoids (lecithin and cholesterin)—traces.	
Carbohydrate	0·5 per cent. sugar.
Inorganic salts	0·6 „

The yolk, which includes the ovum proper, consists of the phospho-protein (vitellin), fat, and lipochrome, with small quantities of sugar, lecithin, cholesterin, and inorganic salts.

MEAT.

Meat consists of muscle with a certain amount of fat, which may be in the connective tissue forming adipose tissue. In pork, the fat is found abundantly in fat cells placed between the muscular fibres, and it is this fat which prevents the easy access of the pepsin-hydrochloric acid to the muscle, hence the indigestibility of pork. The following is the composition of beef:—

Water	76·7 per cent.
Solids	23·3 „
Proteins: myosin gelatin	20 „
Fat	1·5 „
Carbohydrate (dextrose)	0·6 „
Salts	1·2 „

If an individual obtains the necessary 100 grms. of protein from meat, he must consume 500 grms. of meat (just over 1 lb.) *per diem.*

FLOUR.

Brown flour consists of the whole wheat grain, whole flour consists of the grain minus the husk, and white flour consists of the interior of the wheat grain.

Wheat flour has the following composition :—

Water—Small amount.

Solids—Proteins	gliadin ("alcohol soluble") glutelin ("alcohol insoluble")	12 per cent.
Fat		1·4 ,,
Carbohydrate	starch	68·0 ,,
	cellulose	2·5 ,,
Salts		1·8 ,,

The following tables give the composition of some vegetable foods (Halliburton) :—

	Rice.	Lentils.	Peas.	Potatoes.
Water	13·1	12·5	14·8	76·0
Protein	7·9	24·8	23·7	2·0
Fat	0·9	1·9	1·6	0·2
Starch	76·5	54·8	49·3	20·6
Cellulose	0·6	3·6	7·5	0·7
Mineral salts	1·0	2·4	3·1	1·0

The chief points to be noted are—the large amount of starch present, the large proportion of protein in lentils and peas, and the large amount of water in potatoes. The mineral salts are chiefly those of potassium and magnesium.

DOUGH.

Dough is the sticky mass produced when water is added to flour and carefully mixed. The two proteins, gliadin and glutelin, in the presence of water form gluten ; this is the sticky substance which causes the other constituents of flour to adhere.

BREAD.

In bread making, flour, water, and yeast, with a little sodium chloride, are mixed into a dough, and this is set aside in a warm place until it "rises." During this time, an amylolytic enzyme in the yeast converts some of the starch into dextrins and dextrose. The zymase (enzyme) of the yeast then converts some of the dextrose into alcohol and carbon-dioxide, and it is this gas which causes the dough to become spongy and rise. This process is usually allowed to proceed for some few hours. The bread is now baked somewhat rapidly. During the process of baking, the enzymes are killed, and the alcohol and carbon-dioxide are driven off, leaving the bread light and spongy.

Bread consists of—

Water—Variable.	
Solids—Protein (gluten)	7–10 per cent.
Fat	1 "
Carbohydrate (starch, dextrin, dextrose)	55 "
Salts	2 "

The crumb of bread is chiefly starch, whereas the crust contains some starch, dextrin, and dextrose. In pastry making, yeast is omitted, and baking powder (sodium bicarbonate and tartaric acid) substituted; fat in the form of butter or lard is also mixed in.

GREEN VEGETABLES.

These contain—

Water	80–92 per cent.
Solids	8–20 "
Protein	1–2 "
Carbohydrates, including cellulose	3–6 "
Salts, chiefly potassium salts.	

Green vegetables contain a certain amount of nucleo-protein, which contains iron. These nucleo-proteins are called hæmatogens, and are in all probability one of the normal supplies of iron to the body.

BEEF-TEA.

Beef-tea is made by cutting the meat into small pieces, covering it with *cold* water, and adding a little sodium chloride; this is then slowly warmed. The fluid, when poured off, is known as beef-tea, and consists chiefly of water, inorganic salts, and extractives of the meat, such as creatine, hypoxanthine, sarcolactic acid, and traces of protein, but it has very little nutritive value. If the meat extract is made without allowing the temperature to rise to boiling point, there will be a small amount of protein present. If, however, the temperature is raised to boiling point, the protein is coagulated, and is generally strained off.

SOUP.

This is made by putting scraps of meat, bones, and fibrous tissue into a pot, covering them with water and adding salt; the whole is allowed to simmer gently over the fire. The fluid, which is poured off, consists of water, salts, extractives of the meat, and a little protein, chiefly gelatin, which has come from the collagen of the white fibrous tissue. These meat extracts are useful excitants of gastric secretion, especially of HCl, and therefore prepare the way for the digestion of more solid food, such as meat. At the same time, warm soup causes gastric vaso-dilatation, the result of which is a copious secretion of gastric juice. It will be understood then that soup is contra-indicated for persons, who suffer from hyperchlorhydria, or excessive formation of hydrochloric acid by the oxyntic cells of the stomach.

ACCESSORIES.

Tea contains a bitter principle, tannin, and, if tea is allowed to infuse for too long a time, too much tannin goes into solution, and consequently produces dyspepsia. Tea also contains a methyl-purine, theine ($C_5H(CH_3)_3N_4O_2$). China tea contains less methyl-purine than Ceylon tea.

Coffee is rich in aromatic substances, and also contains the methyl-purine, caffeine ($C_5H(CH_3)_3N_4O_2$).

Cocoa, as sold, contains protein and fat, and the methylpurine theobromine ($C_5H_2(CH_3)_2N_4O_2$). It is a food, therefore, because of the large proportion of fat (30 per cent.) and protein (20 per cent.) which it contains.

Tea, coffee, and cocoa are used as stimulants. They are a source of exogenous purines of the body, and of the three coffee is richest in these substances.

COOKING OF FOOD.

The advantages of cooking food are the following:—

1. It renders the food more digestible; steam separates the muscular fibres of the meat and so enables the gastric juice to get at the protein more readily. The insoluble collagen of white fibrous tissue is converted into the soluble gelatin. The cellulose coat of vegetable cells is ruptured, allowing of the easy access of the ptyalin of the saliva to the starch granulose.

2. Micro-organisms, such as tubercle bacilli, round worms, such as trichinæ, and the ova of the flat worms or tapeworms, are destroyed.

3. In the process of cooking, condiments, such as pepper, and other substances, such as salt and sugar, are added which make the food more palatable.

CHAPTER IX.

DIGESTION.

The object of digestion is to convert the food either into a soluble form, or into very small molecules, which are easily absorbed and consequently taken into the blood to be assimilated.

SALIVARY DIGESTION.

The mouth is lined by a mucous membrane, in which there are simple mucous glands which secrete mucin, the function of which is to help to moisten the mucous membrane of the mouth. On to this mucous membrane there are openings of the ducts of the salivary glands which secrete the major portion of the saliva. The parotid gland is a serous salivary gland; the submaxillary and sublingual are mixed salivary glands, that is, they contain both a serous and a mucous portion. Embedded in the substance of the tongue are numerous small simple serous salivary glands which pour their secretion on to the surface of the tongue between the papillæ. These serous and mucous glands, the ducts of which open into the buccal cavity, secrete the saliva. The mucous glands, which are found in the mucous membrane of the mouth, and the serous glands, which are embedded in the tongue, are simple mucous and simple serous glands respectively, but the parotid, submaxillary, and sublingual are compound racemose glands.

STRUCTURE OF THE SEROUS GLANDS.

In order to ascertain the minute structure of these glands, it is essential to examine them under two conditions—

(1) After rest, that is, after the animal has not been digesting food, and (2) after activity, that is, after the animal has been actively digesting food, or after an injection of pilocarpine, a

drug which stimulates the cells of the glands to pour out their secretion.

(*a*) **After rest.**—The unit of the glands consists of an acinus which is made up of a basement membrane, on which are present cubical epithelial cells; these cells line the central lumen of the acinus. If a piece of fresh gland is teased in aqueous humour, and the preparation exposed to the vapour of a 1 per cent. solution of osmic acid, the granules in the cell will be fixed by the osmic acid vapour, and can be readily seen in position, if examined by a high power of the microscope. It will be seen that these zymogen granules, in this particular case ptyalinogen, crowd the inner portions of the cells which line the central lumen, and the nucleus of the cell appears to be pushed away towards the base of the cell.

(*b*) **After activity.**—If, however, a similar preparation of a serous gland is made after actively secreting, it will be found that the cells lining the acinus appear somewhat different; their outline is more distinct, the central lumen becomes more obvious, the granules are fewer, and the nucleus is nearer the inner portion of the cells. That is to say, during activity these cells rapidly pour out the granules which they have been producing and storing up. The ptyalinogen granules readily become converted into the enzyme ptyalin during extrusion from the cell.

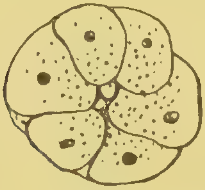


FIG. 7.—Acinus of a serous gland before secretion.

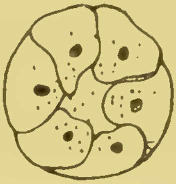


FIG. 8.—Acinus of a serous gland after secretion.

√ STRUCTURE OF A MUCOUS GLAND.

A mucous gland may be examined in a similar way to a serous gland. It will be seen that, if the acinus of a mucous gland is examined after resting, the cells lining the lumen are filled with granules; these are mucinogen granules. If, however, the portion of the gland is teased in a watery stain, the granules disappear, and the part of the cell in which they are becomes swollen and clear. This is due to the conversion of the mucinogen granules into clear mucin. On the surface of the acini of the mucous glands groups of three or four cells may be seen. These cells also contain fine granules, most probably protein in nature, which do not swell when treated with watery stains. These little groups of cells on the margin of the acini form the crescents or demilunes of Gianuzzi, and it is believed that there are minute canals running from these demilunes between the cubical cells of the acini down to the central lumen, so that the secretion of these demilunes can readily escape into the lumen of the acinus.

THE COMPOSITION OF SALIVA.

Saliva is an alkaline fluid of a specific gravity of 1005. It is somewhat viscid because of the mucin which it contains. When freshly secreted, it is practically clear, but on standing soon becomes cloudy, because the CO_2, which it contains, escapes, and the calcium carbonate, which was originally in solution, becomes precipitated. Saliva consists of water 99 per cent., and solids about 0·5 per cent. The important solids are as follows: **Mucin,** which is derived from the mucous glands of the mucous membrane of the mouth, and the mucous portions of the submaxillary and sublingual glands. The mucin may be precipitated by acetic acid. There are also present traces of **serum albumin** and **serum globulin,** and an amylolytic enzyme **ptyalin,** which is derived from the ptyalinogen granules present in the cells of the serous portions of the salivary glands.

Saliva abounds in sodium chloride. It contains also calcium carbonate, a little magnesium phosphate, alkaline sodium phosphate (Na_2HPO_4), and potassium chloride. The saliva derived from the submaxillary gland is particularly rich in calcium salts. This explains the tendency for the deposition of tartar, which contains calcium salts, about the lower teeth, and also explains the greater frequency of salivary calculi in the duct of the submaxillary gland than in the duct of the parotid gland. Saliva also contains a trace of potassium thiocyanate. This is probably one way by which sulphur is eliminated from the body, and, in some diseased conditions of the kidneys, the amount of potassium thiocyanate in the saliva is said to be increased. Its presence may be detected by the fact that it gives rise to a blood-red colour when treated with a trace of ferric chloride solution; this colour, however, is bleached by a solution of mercuric chloride. It should be noted, however, that meconic acid, one of the alkaloids of opium, also gives a blood-red colour with solutions of ferric chloride, but the colour is not dispelled by a solution of mercuric chloride. Saliva contains a relatively large amount of CO_2 in solution. If saliva is examined microscopically, there may be found in it a few loose squamous epithelial cells derived from the buccal mucous membrane; these cells usually contain bacteria. There are also present large round nucleated cells full of granules, which are salivary corpuscles, and are derived from the crypts of the tonsil.

The solid present in the sublingual saliva may be as much as 2·75 per cent.; that in the submaxillary saliva 2·3 per cent.; that in the parotid saliva only about 0·3 per cent.

Sublingual and submaxillary saliva is rich in mucin, but parotid saliva is free from it. It will be seen then that the saliva from the submaxillary and the sublingual glands is rich in a lubricating material, and it is found that all kinds of food produce a flow of saliva from these glands, whereas parotid saliva is most watery, and is abundantly produced by dry food. If an animal is hungry, the sight of dry food is enough to cause a flow of parotid saliva. The nature of food masticated, to a very considerable extent, determines the composition of saliva secreted.

THE NERVOUS MECHANISM OF SECRETION OF SALIVA.

The nerve centre for the secretion of saliva is said to exist in the lower part of the medulla oblongata. This centre is influenced by *afferent* impulses which reach it from various sources—

1. **From the mouth.**—Mechanical irritation of the mucous membrane of the mouth will cause an increased secretion of saliva. Chemical irritation, such as is produced by the presence of acids or salts, will cause an increased flow of saliva. Sweet, sour, bitter, or salty bodies in solution, which are capable of being tasted, will cause an increased flow of saliva. Pawlow has shown that any kind of food causes a

reflex flow of saliva from the submaxillary and sublingual glands, but it is *dry* food that brings about a flow of more watery (parotid) saliva.

2. Psychical impulses from the **brain**, such as the thought of good food, the sight of food, and the smell of it, or hearing about it will cause an increased flow of saliva, provided the individual is hungry.

3. Stimuli reach the centre from the **stomach**, via the vagi, especially when the mucous membrane is in an irritable condition. Before vomiting takes place, there is, as a rule, an increased flow of saliva.

4. Impulses arising in the **abdomen**, and travelling up by the vagus, occasionally cause an increased flow of saliva. A pregnant uterus occasionally causes reflex salivation.

The *efferent* impulses from the centre pass down to the salivary glands through the cervical region of the spinal cord, and up the sympathetic nerves in the neck, and so along the blood vessels to the salivary glands. Impulses also travel down through the glossopharyngeal nerve by its tympanic branch to the tympanic plexus on the mucous membrane of the inner wall of the middle ear. In the case of the submaxillary and sublingual glands, the impulses pass from the tympanic plexus through the facial nerve, thence by its chorda tympani branch to the lingual nerve, thence through the submaxillary ganglion to the sublingual gland, and through Langley's ganglion to the submaxillary gland. In the case of the parotid gland, the impulses pass from the tympanic plexus through the small superficial petrosal nerve, thence through the otic ganglion to the auriculo-temporal nerve, which supplies the parotid gland. If the chorda tympani nerve is cut, and the peripheral cut end stimulated electrically, the result is that the blood vessels in the submaxillary and sublingual glands dilate, and arterial blood leaves the glands. It is found experimentally that the arterial blood pressure in the artery supplying the glands may be as much as 112 mm. Hg, but the saliva in the duct of the submaxillary gland may be secreted against a pressure equal to 200 mm. Hg. The conclusion to be drawn is, that the secretion of saliva may be independent of the arterial blood pressure. Another result of stimulating the peripheral cut end of the chorda tympani nerve is that there is an increased secretion of watery saliva from the duct of the submaxillary gland. If the blood supplied to the gland is cut off, or the animal decapitated, and the peripheral cut end of the chorda tympani stimulated, the result is still an increased secretion of watery saliva for a short time, showing that the chorda tympani contains secreto-motor fibres. If an animal is injected with atropine, which paralyses secreto-excitor fibres in the salivary glands, and the peripheral cut end of the chorda tympani then stimulated, vaso-dilatation still occurs in the submaxillary and sublingual glands, but there is no secretion of saliva. These experiments show that the secretion of saliva normally depends upon a proper blood supply to the gland, and also upon the secreto-excitor mechanism in the chorda tympani nerve, which is quite separate from its vaso-dilator mechanism. If the sympathetic nerve in the neck is cut, and the upper cut end is stimulated, the result is vaso-constriction of the blood vessels in the submaxillary and sublingual glands, and the blood which leaves these glands is of a venous character. Although the blood supply to the gland is diminished, there is found to be an increased secretion of saliva rich in solids; the activity of the cells to pour out their organic constituents is put out of court after the injection of atropine. It is found that, if the submaxillary gland is placed in a plethysmograph, and the peripheral cut end of the chorda tympani nerve is stimulated, although there is a general vaso-dilatation, yet the total result is a shrinkage of the gland because so much fluid is poured out by the cells.

Nerve.	Action upon Blood Vessels.	Action upon Salivary Glands.
Chorda tympani .	Vaso-dilator.	Secreto - excitor of watery saliva.
Sympathetic . .	Vaso-constrictor.	Secreto - excitor of viscid saliva.

Paralytic Secretion.—It is found that, if the chorda tympani nerve is divided on one side, no immediate result with regard to the secretion of saliva takes place; after a few days, however, a small amount of watery saliva is continuously secreted by the glands on the side of section; this is called a paralytic secretion, which may be brought about by the overflow activity of the nerve cells, which are found in the submaxillary and Langley's ganglia, for, after section, these cells are no longer controlled by the central nervous system. It has been suggested, however, that the increased secretion is due to the increased irritability of the nerve fibres analogous to the fibrillary twitchings in degenerating muscle, after the nerves to it have been cut, and before complete degeneration occurs. It is said that, after section of one chorda tympani, there is an increased secretion of watery saliva on the other side; this is called the *antilytic* secretion. Section of the sympathetic nerve in the neck does not cause analogous phenomena, nor does it stop the paralytic secretion which has been brought about by the section of the chorda tympani nerve.

THE SUBMAXILLARY AND LANGLEY'S GANGLIA.

The submaxillary ganglion is connected with the lingual nerve. It consists of a number of ganglion cells, which give rise to fibres which travel to the sublingual gland. The submaxillary ganglion receives nerve fibres from the chorda tympani, which travel *via* the lingual. It is traversed by nerve fibres which travel down to Langley's ganglion, which is placed in the hilum of the submaxillary gland. This

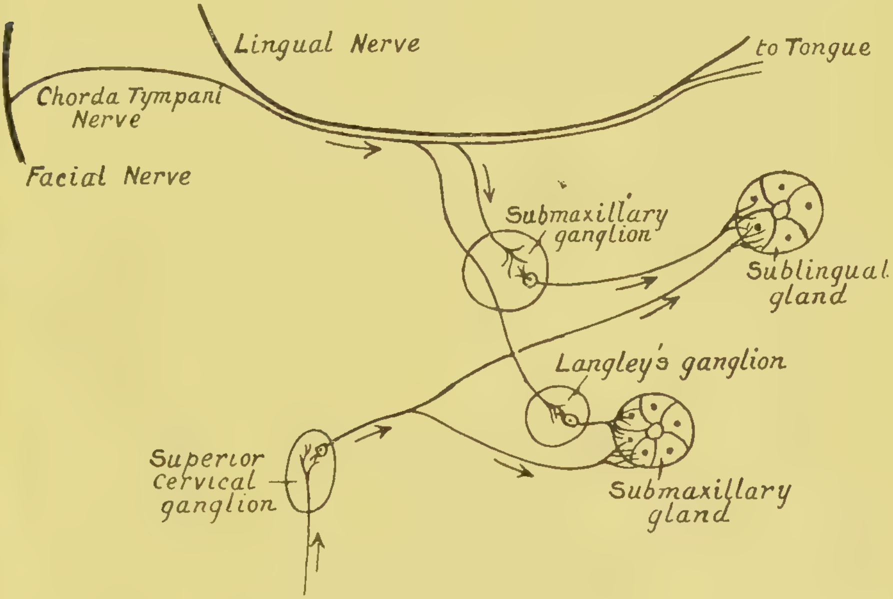


FIG. 9.—Diagram of secretory nerves to the submaxillary and sublingual glands.

ganglion contains nerve cells which give rise to fibres which travel to the submaxillary gland. It has been shown, by Langley's nicotine method, that these ganglia are cell stations where synapses occur between the cerebral fibres and the ganglion cells which innervate the glands. Nicotine, applied locally, poisons these fine synapses and nerve cells. If the submaxillary ganglion is painted with nicotine, and the chorda tympani nerve is stimulated, it is found that no impulses get through to the sublingual gland, because they are blocked in the submaxillary ganglion, but impulses will travel through to the submaxillary gland. If, however, Langley's ganglion is painted with nicotine, and the chorda tympani nerve is stimulated, the impulses will not travel through to the submaxillary gland, because the impulses have been blocked in the ganglia. It was by experimenting in this way that Langley showed that the submaxillary ganglion is a cell station for the sublingual gland, and that Langley's ganglion is the cell station for the submaxillary gland.

THE FUNCTIONS OF SALIVA ARE—

1. To moisten and lubricate the mucous membrane of the mouth and tongue, and therefore to assist in speech.

2. To moisten and lubricate the solid particles of food, to stick the portions of masticated food together, and consequently to help to form the bolus. The bolus of food is lubricated with the mucin, and so prepared for being swallowed.

3. To dissolve soluble substances like sugar, salts, acids, and bitter substances, and therefore to render them capable of being tasted.

4. By the action of its amylolytic enzyme, ptyalin, to convert cooked starch into maltose, a change which may be readily demonstrated in a test-tube. A solution of starch is made by boiling, and, in this way, the starch cellulose coating is ruptured, and the starch granulose set free. If the solution is cooled, and a drop of a weak solution of iodine added, it will be found that it gives a blue colour. If to this starch solution some saliva is added, and kept at a temperature of 40° C., the starch gradually disappears, and is replaced by erythro-dextrin and achroö-dextrin, the former of which gives a reddish colour on the addition of a drop of solution of iodine. The achroö-dextrin gives no distinct colour when a

drop of solution of iodine is added, but may be precipitated from its solution by 85 per cent. alcohol. Gradually the erythro-dextrin disappears, and some achroö-dextrin remains together with a reducing sugar, maltose. At this stage no colour is produced when a drop of iodine solution is added. This is called the *achromic point*, and indicates that all the starch and erythro-dextrin have disappeared. The final products are achroö-dextrin and maltose, a reducing sugar which gives the ordinary reducing sugar tests.

$$\underset{\text{(Starch)}}{10(C_6H_{10}O_5)_n} + 4(H_2O)_n = \underset{\text{(Erythro-dextrin)}}{(C_6H_{10}O_5)_n} + \underset{\text{(Achroö-dextrin)}}{(C_6H_{10}O_5)_n} + \underset{\text{(Maltose)}}{4(C_{12}H_{22}O_{11})_n}$$

As a rule, starch does not remain long enough in the mouth for this change to be completed, but the action of the ptyalin, swallowed with the food, is continued in the stomach for about twenty minutes or longer; it is then stopped by the secretion of the free hydrochloric acid of the gastric juice. The food passes quickly between the pillars of the fauces and the œsophagus, and no further digestive change takes place until it gets into the stomach.

CHAPTER X.

GASTRIC DIGESTION.

THE POSITION AND SHAPE OF THE STOMACH.

Recent researches carried out by Arthur F. Hertz show that the normal position and shape of the stomach differ from what was formerly described. Hertz administers to the individual under observation the oxychloride of bismuth, as this salt is chemically inert in the stomach, and it does not interfere with the important mechanism by which the hydrochloric acid of the gastric juice influences gastric peristalsis and controls the activity of the pylorus. The individual is given two ounces of bismuth oxychloride in bread and milk, and the stomach is then examined by means of X-rays. Such an examination demonstrates that, in the *upright* position of the body, the stomach lies in the position as is shown in Fig. 10.

It will be seen that the greater curvature extends below the umbilicus; the distance below the umbilicus is on an average 5·5 cms. This is found to be the case in the majority of individuals who take an ordinary amount of food. In the horizontal position of the body Hertz and Morton have shown that the lowest part of the greater curvature is just *above* the umbilicus.

The *fundus* of the stomach lies above a horizontal plane passing through the cardiac orifice (His). It is somewhat hemispherical in shape, lies in the concavity of the left half of the diaphragm, and it nearly always contains gas. The *body* of the stomach is almost vertical; it is nearly uniform in width, and is situated to the left of the middle line. The fundus and body constitute the cardiac or larger portion of the stomach. The distinction between the cardiac and pyloric portions is not very definite, but the separation of the cardiac from the pyloric portions may be recognised in frozen and in formalin-fixed specimens, and also by the use of X-rays, by the presence of the *incisura angularis* upon the smaller curvature, and by a less constant depression upon the greater curvature (*vide* Fig. 10).

The pyloric part of the stomach consists of the pyloric vestibule and the pyloric canal.

The *pyloric vestibule* is directed upwards and slightly backwards as it turns to the right. This portion of the stomach extends to the right of the middle line. The pyloric vestibule is continuous with the *pyloric canal* (Jonnesco). This last-named portion of the stomach is definitely tubular, and is about 3 cms. long. It makes a sharp angle with the pyloric vestibule as it passes upwards and backwards, where it comes in contact with the liver. The pyloric canal is relatively long in infants, and in them its separation from the pyloric vestibule is sharper than in adults. Its termination projects into the duodenum, producing, as Cunningham has pointed out, a striking resemblance to the portio vaginalis of the cervix uteri (*vide* Fig. 11).

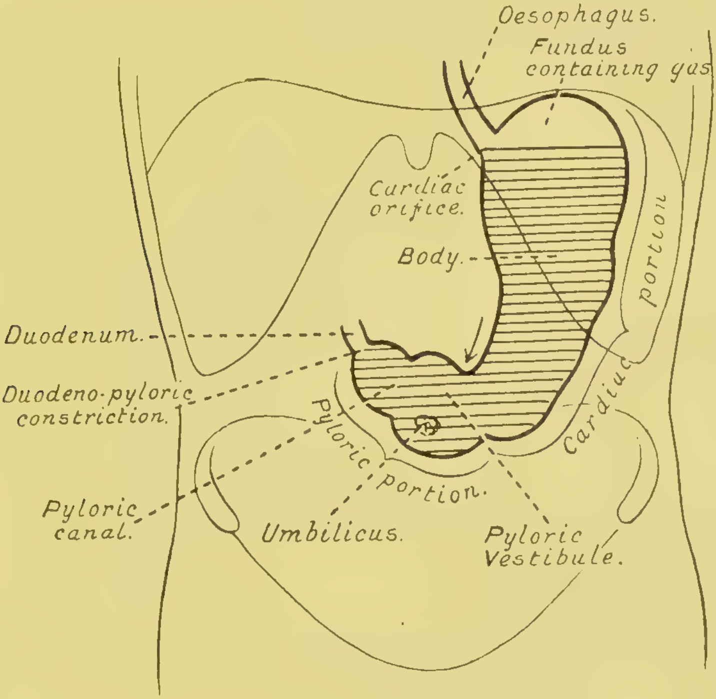


FIG. 10.—The position of the stomach in the erect posture of the body. The arrow is directed to the incisura angularis. (*After* Arthur F. Hertz.)

THE STRUCTURE OF THE STOMACH.

The stomach is covered on the outside by the peritoneum, beneath which is subperitoneal tissue.

The muscular coat consists of three distinct portions—the *longitudinal* fibres, which are most readily seen at the smaller and greater curvatures, the *circular* muscle fibres, which are the most obvious at the middle and at the pyloric canal, here forming the pyloric sphincter, and the *obliquely set* muscular fibres, which are continuous with the circular muscular fibres of the œsophagus, and which form a kind of cardiac sphincter and extend over the fundus and body of the stomach. Both the circular and longitudinal muscular coats are much thicker in the pyloric canal than in any other part of the stomach. The circular fibres are arranged in the form of a sphincter, which attains to its greatest development at the junction with the duodenum, where it is separated by a distinct connective tissue septum from the circular coat of the duodenum. Only a few of the more superficial longitudinal fibres are continuous with those of the duodenum, the majority forming distinct fasciculi, which penetrate the substance of the sphincter, in which some end, whilst others reach the subjacent submucous tissue (A. F. Hertz). Internal to the muscular coat is the submucous coat, which contains the blood vessels and the

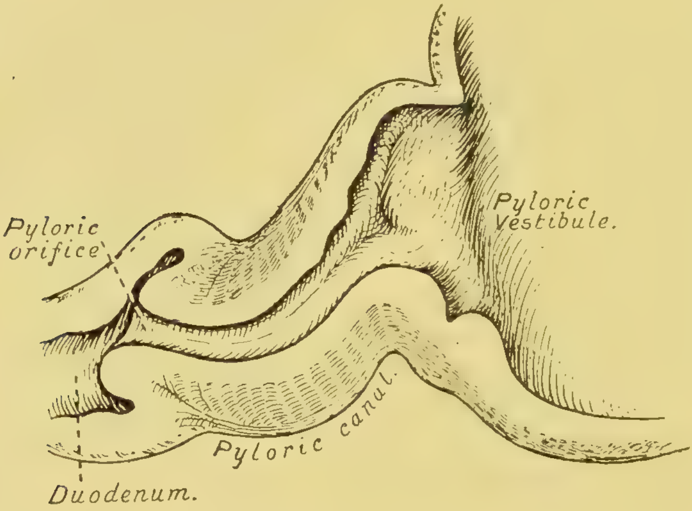


FIG. 11.—Pyloric vestibule, pyloric canal, and pyloric orifice of stomach. (*After* Arthur F. Hertz.)

lymphatics, and circular and longitudinal plain muscular fibres, forming the muscularis mucosæ, which produces the rugæ or folds of the mucous membrane. Internal to this is the mucous membrane.

In the mucous membrane are three sets of tubular glands—

(*a*) The **cardiac glands**, found near the cardiac orifice; these are simple tubular glands, lined by cubical epithelial cells, and in all probability secrete mucin.

(*b*) The **fundus glands**, found over the fundus and body of the stomach. These have short ducts lined by columnar epithelial cells. Opening into the duct, there are usually two gland tubes, of which the neck of each is somewhat constricted. The duct and neck of these glands are lined by columnar cells. The lumen and the more dilated fundus portion of the tube is lined by two kinds of cells; on the basement membrane are the scattered ovoid, or parietal cells, or oxyntic cells, so called because they secrete free hydrochloric acid. Over these cells are placed the columnar or chief cells. The columnar cells are coarsely granular, and help to secrete the gastric juice. It is believed that there are minute passages between these columnar cells down to the ovoid, or parietal cells, by which free hydrochloric acid may arrive at the lumen of the tube.

(*c*) The **pyloric glands**, found at the pyloric portion of the stomach, have long ducts lined by columnar cells. The secreting part of the tube is shorter, has a narrow neck, and is lined by cubical cells. The fundus is lined by flattened columnar cells, which are not so coarsely granular as the columnar cells found at the fundus of the fundus glands. The pyloric glands become larger as they approach the pylorus, and, through the pyloric orifice of the stomach, they become directly continuous with the small racemose glands of Brunner, which occur in the submucous coat of the duodenum. The pyloric glands probably produce a chemical stimulant, or hormone, called *gastric secretin*, and this causes the continued secretion of gastric juice by the fundus glands (*vide* p. 293).

Pepsin and rennin are enzymes, which occur in the gastric juice, and are derived from zymogen granules, which are secreted by the central or chief cells of the fundus glands and the columnar cells of the pyloric glands. In the case of pepsin, the particular zymogen, or enzyme precursor, is called pepsinogen.

THE BLOOD SUPPLY OF THE MUCOUS MEMBRANE OF THE STOMACH.

The arterioles ramify in the submucous tissue of the stomach. These give off the intertubular capillaries, which run into the mucous membrane between the gastric glands. Here these intertubular capillaries form a deep plexus, which opens into a superficial plexus of capillaries just beneath the surface of the mucous membrane. The veins commence in the superficial plexus, and run out to open into the small veins found in the submucous tissue.

THE METHODS OF OBTAINING GASTRIC JUICE.

1. The mucous membrane of the stomach of the pig may be dissected off through the submucous tissue. It should be kept in a glass vessel and covered with glycerin. In this way, a glycerin extract of pepsin may be obtained, and this extract will remain active for a considerable time. When this glycerin extract is used for artificially digesting protein, a little 0·2 per cent. hydrochloric acid must be added.

2. In the œsophagus of a dog a fistula is made so that food swallowed escapes at the artificial opening, and does not enter the stomach. A gastric fistula is also made between the stomach and the skin, and, from this, when meat is given to the dog, it is swallowed, and recovered through the artificial œsophageal opening, but gastric juice is secreted and may be obtained from the gastric fistula.

3. A small piece of stomach is dissected from the main portion, and sutured to the skin of the abdomen. This little sac of stomach is separated from the main stomach by a septum of mucous membrane, its blood supply and nerve supply being kept intact. The animal may be fed in the ordinary way, and pure gastric juice obtained from the fistulous opening in the little stomach.

MECHANISM OF SECRETION OF GASTRIC JUICE.

The secretion of gastric juice is to a considerable extent under the control of the central nervous system, because, as is well known, sudden emotion frequently inhibits the secretion of the juice and upsets digestion. It has been shown that even the psychic element obtains in the dog. If a dog is hungry, and is shown meat, and it is under the impression that it is going to have the meat, there is an increased secretion of gastric juice, as is shown by the increased flow from the small stomach, as mentioned above; but if the dog understands that it is not to have the meat which it sees, the flow of gastric juice is inhibited. It is said that, when an individual is hungry, the smell of good food being cooked and the sight of appetising articles of food are sufficient to produce a secretion of gastric juice. The early juice secreted is called "appetite juice," and is of value in starting the process of digestion. The nervous impulses travel down from the central nervous system through the vagus nerves (Pawlow), for it has been found that, if the vagus nerve is cut in the neck, and allowed to remain for five days before it is stimulated in order that the cardiac branches to the heart may degenerate, and if, at the end of this time, the peripheral end is stimulated, it is found that the heart is not inhibited, but, after a long latent period, there is a secretion of gastric juice. The peripheral endings of the secretory fibres of the vagus may be paralysed by atropine. The vagus then contains two sets of fibres to the mucous membrane of the stomach—the *secreto-excitor* and *secreto-inhibitory* fibres. It is said that these phenomena occur after the splanchnic nerves have been divided, and hence it is surmised that they do not contain secretory fibres. It is believed, however, that the normal stimulus for secretion of gastric juice is a chemical one, such as alkali, which is swallowed with the saliva, or it may be that dextrin (a peptogen), obtained from the partially digested starch, acts as a stimulus and causes the mucous membrane at the pyloric end of the stomach to produce gastric secretin or *gastrin* (Edkins), which stimulates the cells of the fundus glands to pour out pepsin-hydrochloric acid. The products of proteolysis are peptogenic, and cause more gastric juice to be secreted. Bitters cause a production of "appetite juice" probably by stimulating the gustatory nerves.

CHARACTERS OF GASTRIC JUICE.

Pure gastric juice is a clear colourless acid dextro-rotatory fluid, of which the specific gravity varies between 1003 and

1006. It contains water 99 per cent., and solids about 1 per cent. The chief constituents of the gastric juice are—

Pepsin (0·3 per cent.), a proteoclastic enzyme.
Rennin, a coagulative enzyme which acts upon caseinogen.
Gastric lipase, a lipolytic enzyme.
Mucin produced by the goblet cells of the gastric mucous membrane.

Free hydrochloric acid	0·2 per cent.
Inorganic salts	0·2 ,,
$NaCl$	0·14 ,,
KCl	0·05 ,,
$CaCl_2$	0·006 ,,
$Ca_3(PO_4)_2$ $Mg_3(PO_4)_2$ $FePO_4$	0·01 ,,

If lactic acid is present, it is due to fermentation. The gastric juice of carnivorous animals is richer in solids, and more powerful than the gastric juice of man. The composition of gastric juice depends, to a very considerable extent, upon the kind of food which excites it. Meat causes a large secretion of gastric juice, rich in hydrochloric acid. Bread causes the secretion of a small amount of juice, rich in pepsin, but poor in acid. Finely divided fat, such as exists in milk, causes a delay in gastric secretion.

The pepsin is derived from the pepsinogen granules which are found in the columnar and cubical cells lining the gastric glands, and probably the rennet enzyme is derived in a similar way. The free hydrochloric acid is secreted by the oxyntic, parietal, or ovoid cells, which are found on the basement membrane of the fundus glands. These ovoid cells are very numerous in the mucous membrane of the stomach of the dog, and they are readily demonstrated by staining with aniline dyes, such as eosin which stains them red, and methylene-blue and toluidine-blue which stain them blue.

The formation of hydrochloric acid by these cells is no doubt the result of their biotic activity. Maly suggests that its formation may be the result of the interaction of alkaline sodium phosphate and calcium chloride brought about by these cells as follows:—

$$2Na_2HPO_4 + 3CaCl_2 = Ca_3(PO_4)_2 + 4NaCl + 2HCl$$

On the other hand, it is quite possible that the formation of free hydrochloric acid may be due to the action of the carbonic acid of the blood upon akaline sodium phosphate, the alkaline sodium phosphate being thus converted into acid sodium phosphate, which acts upon the sodium chloride which is taken into the stomach with the food, and forming alkaline sodium phosphate and hydrochloric acid, thus—

(*a*) $Na_2HPO_4 + H_2O.CO_2 = NaH_2PO_4 + NaHCO_3$
(*b*) $NaH_2PO_4 + NaCl = Na_2HPO_4 + HCl$

Whichever chemical view is taken, there is no doubt that the change is brought about by the oxyntic cells, and the free hydrochloric acid, so produced, passes along into the lumen of the fundus glands and so into the stomach. The following are the chief tests to prove the presence of free hydrochloric acid in the gastric juice:—

(*a*) One drop of filtered gastric juice and one drop of Günzburg's reagent (vanillin, pt. 1; phloro-glucinol, pts. 2; rectified spirit, pts. 30) are mixed together on a glass slide and gently warmed until evaporation takes place. Red crystals are produced if free hydrochloric acid is present in the filtered gastric juice. If much peptone is present a red paste is obtained. This reaction is said to detect one part of free hydrochloric acid in 10,000. Organic acids do not give this reaction.

(*b*) *The Tropæolin Test.*—One drop of tropæolin-oo in 94 per cent. methylated spirit is evaporated at 40° C. in a white capsule. This leaves a brownish stain. A glass rod is then dipped into filtered gastric juice, and with it the brown stain is touched. If free hydrochloric acid is present a brilliant violet colour is produced at the place of contact. This test detects 0·006 per cent. of free hydrochloric acid. Other inorganic acids give this reaction, but organic acids do not.

(*c*) *Töpfer's Test.*—One drop of dimethyl-amino-azo-benzene is allowed to run over a white capsule. If a drop of filtered gastric juice is added, which contains a trace of free hydrochloric acid, a bright red colour is produced.

TESTS FOR LACTIC ACID.

Lactic acid may be extracted from gastric juice by ether, and detected by one of the following methods:—

(*a*) *Uffelmann's Fluid* is a violet solution made by taking 10 c.c. of a 1 in 20 solution of carbolic acid, and adding to it 20 c.c. of distilled water and 1 drop of a solution of ferric chloride. If a trace of lactic acid is added to this violet solution, the colour disappears and the solution acquires a yellowish tint. This reaction is said to detect 1 part of lactic acid in 10,000.

(*b*) *Hopkins' Test.*—A trace of lactic acid is put into a dry test-tube, and 5 c.c. of concentrated sulphuric acid are added, then 3 drops of a saturated solution of copper sulphate. These are gently mixed, and the test-tube kept warm in hot water for four minutes. It is then cooled under the tap. A drop of a 0·2 per cent. alcoholic solution of thiophene is added, and the mixture again warmed; a pink colour is produced.

THE ACTION OF GASTRIC JUICE.

1. **On Protein Food.**—The large protein molecule is acted upon by the pepsin-hydrochloric acid, and is by proteolysis converted into simpler substances, that is, proteoclastic changes are brought about. The first substance produced is one of the nature of a soluble globulin which coagulates at 56° C.; acid meta-protein is next produced. The next stage is the formation of primary proteoses of which there are two—proto-proteose, soluble in water, and hetero-proteose, insoluble in water, but soluble in normal saline solution.

These primary proteoses may be precipitated from their solution by saturation with magnesium sulphate crystals, or by saturation with sodium sulphate crystals, or by half-saturation with ammonium sulphate solution.

Deutero- or secondary proteose is then produced. It is soluble in water, is not precipitated by saturation with magnesium sulphate, sodium sulphate, or half-saturation with ammonium sulphate, but is precipitated by complete saturation with ammonium sulphate crystals. If the original protein, which is digested by the pepsin-hydrochloric acid, is gelatin, then gelatinose is produced. The term proteose is a general one, including albumose from albumin, globulose from globulin, vitellose from vitellin, elastose from elastin. The final stage of gastric digestion of protein food is the formation of peptone, which is probably a mixture of polypeptides. This is not precipitated by saturation with neutral salts, but may be precipitated by alcohol, by tannic acid, by phospho-tungstic acid, and by phospho-molybdic acid. Both the proteoses and the peptones give the biuret reaction. There is a fair proportion of unpeptonised protein leaving the stomach in the acid gastric chyme, which is shot through the pylorus into the duodenum.

PROTEIN
|
acted upon by pepsin-hydrochloric acid
|
Soluble globulin
|
Acid meta-protein
|
Proteoses or propeptone
- primary proteose
  - proto-proteose
  - hetero-proteose
- secondary or deutero-proteose

|
Peptone

Peptone, a mixture of polypeptides, is usually considered to be the end product of the action of the enzyme, pepsin, upon protein. If sufficient time is allowed for the further action of pepsin, amino-acids are produced.

2. **The Action upon Caseinogen of Milk.**—The chief protein of milk is caseinogen, which is present combined with a soluble calcium salt forming calcium caseinogenate. The rennin of the gastric juice converts this soluble caseinogenate into soluble casein. The soluble casein, thus produced, reacts with the soluble inorganic calcium salts present, such as calcium chloride, to form the insoluble casein or caseate of lime which is the curd. It might be asked why it is that the chief protein of milk must be curdled before it is digested. The reason is that the semi-solid curd produced will remain in the stomach longer, and therefore enable the pepsin-hydrochloric acid to digest it, just as ordinary protein is digested, the final product being peptone.

3. **The Action on Fat.**—The gastric lipase splits emulsified fat to a great extent into glycerine and fatty acid, and it is found that the finer the emulsion is, the more intimate is the mixture with the gastric juice, and the greater the action of this lipase. The pancreas is inactive in the case of infants, who, therefore, depend upon this fat-splitting enzyme of the gastric juice for the digestion of fat. According to Pawlow, the consumption of a large amount of fat tends to inhibit the secretion of gastric juice, and this may partly account for the dyspepsia which follows the swallowing of pork. The protein

envelope which surrounds the fat of connective tissue is digested by the pepsin-hydrochloric acid, and, in a similar manner, the calcium caseinogenate envelope around the minute globules of fat in milk is also digested so that much of the confined fat swallowed is freed in the stomach, and split by the gastric lipase. Some of the contents of the duodenum containing bile and pancreatic juice are said to be regurgitated into the stomach through the pylorus, and in this way more fat is digested in the stomach than can be accounted for by the small amount of gastric lipase which is present. If oil is given by the mouth when the stomach is empty, it inhibits the secretion of gastric juice, and as soon as a little reaches the duodenum it excites the flow of bile and pancreatic juice, with which some of it regurgitates into the stomach (A. F. Hertz).

4. **The Action upon Carbohydrates.**—Gastric juice has no action upon starch, but in virtue of the free hydrochloric acid it may aid in the solution of the cellulose coating of the starch granule, and so prepare the starch for the action of the amylopsin of the pancreatic juice. The amylolytic action of the ptyalin of saliva is checked by hydrochloric acid. Cane sugar is inverted into dextrose and lævulose, and in a similar manner there may be some slight action on the other disaccharides, some of the maltose produced by the saliva being converted into dextrose, and some of the lactose of milk being converted into dextrose and galactose.

In virtue of its free hydrochloric acid, gastric juice has an important **antiseptic action,**—many bacteria, which are swallowed with the food, being killed, and in this way hydrochloric acid prevents putrefactive changes taking place in the stomach.

The acid gastric chyme, produced by the action of the gastric juice upon the various kinds of food, is gradually allowed by the pyloric sphincter to escape into the duodenum, where it is further acted upon by other digestive juices with which it comes into contact. The hydrochloric acid which escapes into the duodenum aids in the production of secretin. Its presence in the duodenum also helps to regulate the pyloric sphincter. Von Mering injected acid into the duodenum, and so caused closure of the pyloric orifice. The gastric juice does not digest the wall of the stomach, because the epithelial cells secrete an anti-body called anti-pepsin, which neutralises the action of the pepsin. The following may in part explain the formation of acute gastric ulcers. The mucous membrane of the stomach in the neighbourhood of the pylorus where these ulcers usually occur is particularly liable to injury during digestion, and it may be that such injured and inflamed cells are no longer capable of producing the anti-pepsin; hence they are liable to be rapidly digested, and the local digestive process once begun progresses rapidly with the formation of a deep ulcer.

CHAPTER XI.

PANCREATIC DIGESTION.

THE STRUCTURE OF THE PANCREAS.

THE pancreas consists of two portions :—

1. The tubulo-racemose part.
2. The cell islets of Langerhans.

The tubulo-racemose portion is very much like a serous salivary gland in structure, and consists of elongated or tubular acini, each of which is lined by large cubical cells placed on the basement membrane. These cells line the central lumen, but internal to these cells are occasionally found spindle-shaped cells, known as the centro-acinar cells. If the pancreas of a recently killed animal, such as a guinea-pig, is examined in the fresh state, it will be seen that the cells lining the acini are full of minute granules. These granules occupy the innermost portions of the cells, and the nuclei appear to be pushed towards the basement membrane. This is the resting condition of the pancreas. If, however, a 1 per cent. solution of the nitrate of pilocarpine is injected into the peritoneal cavity of a guinea-pig, and the animal is killed half an hour afterwards, and a portion of the fresh pancreas, first teased in aqueous humour, is then exposed to the vapour of a 1 per cent. solution of osmic acid, it will be seen that the cells lining the acini are smaller and the granules are fewer than in the resting state. The effect of the pilocarpine is to cause the cells to pour out their zymogen granules.

In the inter-acinar connective tissue of the pancreas there are irregular masses of spheroidal or cuboidal cells the protoplasm of which is not nearly so granular as in the cells lining the acini. These irregular islets of epithelial cells are known as the cell islets of Langerhans; they are well supplied with blood, and are not connected with any duct. It appears that they are developed separately from the tubulo-racemose portion, and that in certain fish they exist as separate bodies. It is said that these cell islets produce an internal secretion which is extremely important in carbohydrate metabolism. Opie has advanced the view that, when diabetes mellitus occurs as the result of pancreatic disease, it is the cell islets which are damaged, and that these are therefore responsible for the disturbed carbohydrate metabolism. On the other hand, Dale states that these cell islets are being continuously formed directly from the acini of the pancreas itself. By the injection of secretin he was able to cause increased production of large cell islets in the pancreatic tissue (*vide* p. 290).

METHODS OF OBTAINING PANCREATIC JUICE.

1. The pancreas of an animal, recently killed, is minced and extracted with water. This extract, however, soon decomposes.

2. A fresh pancreas is minced a few hours after death, and a glycerin extract made.

3. A cannula is placed in the pancreatic duct of a dog before the duct enters the duodenum; in this way fresh pancreatic juice may be obtained as follows. The mucous membrane of the duodenum or jejunum of a dog recently killed is carefully removed, and this is extracted with normal saline solution. The salt dissolves out a substance called *pro-secretin*, which is produced in the mucous membrane of the upper part of the small intestine. To this salt extract is added a little 0·2 per cent. hydrochloric acid, the effect of which is to cause the pro-secretin to split off an active substance—*secretin*. The same change may be brought about by boiling the salt extract of the mucous membrane. If this solution of secretin is introduced into the jugular vein of the dog, in the pancreatic duct of which the cannula is fixed, the effect of the secretin will be to stimulate the cells of the pancreas to pour out their contents, and in this way an appreciable amount of pancreatic juice may be obtained through the cannula (*vide* p. 292).

CHARACTERS OF PANCREATIC JUICE.

Fresh pancreatic juice is a somewhat thick colourless solution strongly alkaline, of specific gravity 1007. It contains water, from 90 to 96 per cent. The solids in solution are chiefly the following salts: Sodium chloride, sodium carbonate, alkaline sodium phosphate, calcium phosphate, and magnesium phosphate. It contains the zymogen, trypsinogen, which is activated by the zymolysin or enterokinase of the succus entericus; this converts the inactive trypsinogen into a very active proteolytic enzyme trypsin. The enzymes present are amylopsin or pancreatic diastase, and pancreatic lipase. Stale pancreatic juice contains leucine and tyrosine, which are some of the products of proteolysis. About 500 to 600 c.c. of pancreatic juice are secreted in twenty-four hours.

COMPOSITION OF PANCREATIC JUICE.

Water	90 to 96 per cent.
Solids	4 to 10 „
Enzymes . .	Trypsin, a proteolytic enzyme.
	Amylopsin, an amylolytic enzyme.
	Pancreatic lipase, a lipolytic enzyme.
Salts . .	Chlorides of sodium and potassium.
	Carbonate of sodium.
	Phosphates of sodium, calcium, magnesium.

It is generally held that the composition of the pancreatic juice remains fairly constant, and does not particularly adapt itself to the various kinds of food digested. The amount of pancreatic juice secreted depends directly upon the amount of secretin formed, and this in turn depends upon the amount of hydrochloric acid arriving in the duodenum from the stomach.

MODE OF SECRETION OF PANCREATIC JUICE.

After food is taken the amount of pancreatic juice secreted gradually rises, and is at its maximum about the third hour; the amount of secretion then gradually diminishes, and is said to fall to zero at the end of the fifth hour, unless, of course, more food is taken. Pawlow maintains that the secretion of pancreatic juice is under the control of the central nervous system, and that the vagus is the chief efferent nerve; but it is also stated that the sympathetic nerve has some secretory fibres for the pancreas, and it is possible that the vagus also contains some secreto-inhibitory fibres. Starling and Bayliss have shown that the secretion of pancreatic juice is not a reflex nervous secretion, but, in ordinary circumstances, is due to a local chemical mechanism. They cut the vagus nerve of a dog and then destroyed the local ganglia, then increased the secretion of pancreatic juice by injecting into the blood stream of the animal a saline extract of the mucous membrane of the duodenum of another dog recently killed. This extract had been previously treated with a little weak hydrochloric acid. It is concluded, then, that the sodium chloride in the acid gastric chyme dissolves out an inactive substance called *pro-secretin*, which is produced by the cells in the mucous membrane of the duodenum and jejunum, and that this pro-secretin is further acted upon by the free hydrochloric acid which is present in the acid gastric chyme. In this way the active organic substance *secretin* is split off from the pro-secretin. The secretin is then absorbed locally, and carried by the blood stream to the pancreas, where it stimulates the cells of the pancreas to pour out their contents. If the animal is placed under the influence of atropine this secretory mechanism is not put out of court. It is quite possible, therefore, that the secretion of pancreatic juice is normally brought about by a local chemical mechanism, which in its turn depends upon the acid gastric chyme; but that this local mechanism, to a certain extent, is controlled by the central nervous system through the vagus nerves. According to Dixon and Hamill, the cells of the pancreas produce three zymogens—*protrypsinogen*, *proamylopsin*, and *prolipase*, and the secretin absorbed acts on all, liberating trypsinogen, amylopsin, and lipase. In the intestine the trypsinogen is converted into active trypsin by the enterokinase of the succus entericus.

Pro-secretin also gives rise to another substance besides secretin. This other body lowers arterial blood pressure, and it is quite possible that it is absorbed by the mucous membrane of the small intestine, and carried in the blood stream to the pancreas, where it produces a local vasodilatation of the arterioles, a flushing of the capillaries, and consequently an increased activity of the cells of the pancreas. These substances, derived from pro-secretin, have a similar action upon the liver, causing vasodilatation and an increased production of bile.

THE ACTION OF PANCREATIC JUICE.

1. **Upon Protein.**—It is found experimentally that pancreatic juice, obtained by a cannula placed in the pancreatic duct, has no action whatever upon protein food. It will be remembered that absolutely fresh pancreatic juice contains the inactive zymogen, trypsinogen, but in the intestine the inactive trypsinogen is activated by enterokinase, or zymolysin, which occurs in the succus entericus, and is thus converted into active trypsin,—that is to say, in the intestine, pancreatic juice, in the presence of succus entericus, is actively proteoclastic, or capable of splitting protein. The protein is acted upon by the trypsin in the presence of the alkali sodium carbonate ; it is first converted into a smaller molecule of the nature of a soluble globulin, then into alkaline meta-protein. This is further split into the proteoses, one of which is readily demonstrable, namely, deutero-proteose. This is still further split into the still smaller molecule peptone, probably a mixture of polypeptides. In the small intestine the pancreatic juice does not act by itself, but needs the presence of succus entericus, when the erepsin aids the trypsin in further breaking the peptone molecule into individual polypeptides, which are linkage bodies containing two or more amino-acids. These polypeptides are further broken into the more soluble amino-acids, such as leucine (amino-caproic acid), tyrosine (oxy-phenyl-amino-propionic acid), aspartic acid (amino-succinc acid), glutamic acid (amino-pyro-tartaric acid). Besides the amino-acids the hexone bases are produced. These are lysine (diamino-caproic acid), arginine (guanidin-amino-valeric acid), and histidine (imidazol-amino-propionic acid) ; and lastly, amongst the cleavage products of proteolysis, are tryptophane (indole-amino-propionic acid) and ammonium compounds. By the result of bacterial action in the intestine some of the amino-acids are further split into aromatic substances, indole (C_8H_7N), skatole (β-methyl-indole), and phenol. Tryptophane itself is decomposed by the bacteria of putrefaction into indole and skatole (β-methyl-indole), and tyrosine gives rise to phenol.

PROTEIN
Acted upon by trypsin-sodium carbonate
|
Soluble globulin
|
Alkaline-meta-protein
|
Deutero-proteose
|
Peptone
|
Polypeptides
|
Mono-amino acids (leucine, aspartic acid, glutamic acid)
Diamino acids (lysine, arginine)
Aromatic amino-acids (tyrosine, tryptophane)
Ammonium compounds.

These units of the complex protein molecule are in all probability set free *in the intestine* by the aid of the enzyme, erepsin, which is present in the succus entericus.

In a similar manner trypsin-sodium carbonate digests gelatin, though it has practically no digestive action on collagen.

TEST FOR LEUCINE ($C_5H_{10}.NH_2.COOH$), OR AMINO-CAPROIC ACID.

It forms spheroidal clumps of colourless crystals, which may occur separately.

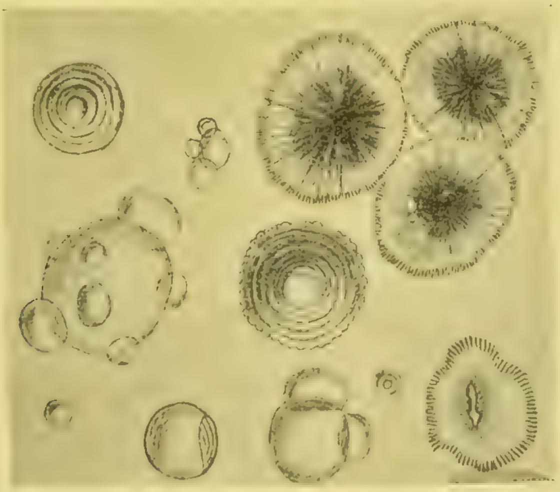


FIG. 12.– Leucine crystals. (Halliburton, *after* Kühne.)

TESTS FOR TYROSINE ($(C_6H_4.OH)C_2H_3.NH_2.COOH$) OXY-PHENYL-ALANINE, OR OXY-PHENYL-AMINO-PROPIONIC ACID.

1. It forms fine colourless needle-shaped crystals, often seen in bundles.

2. Tyrosine gives a red colour with Millon's reagent.

3. Mörner's test.—If pure tyrosine is boiled with Mörner's solution (formalin 1 c.c., distilled water 45 c.c., concentrated sulphuric acid 55 c.c.) an emerald green colour is produced.

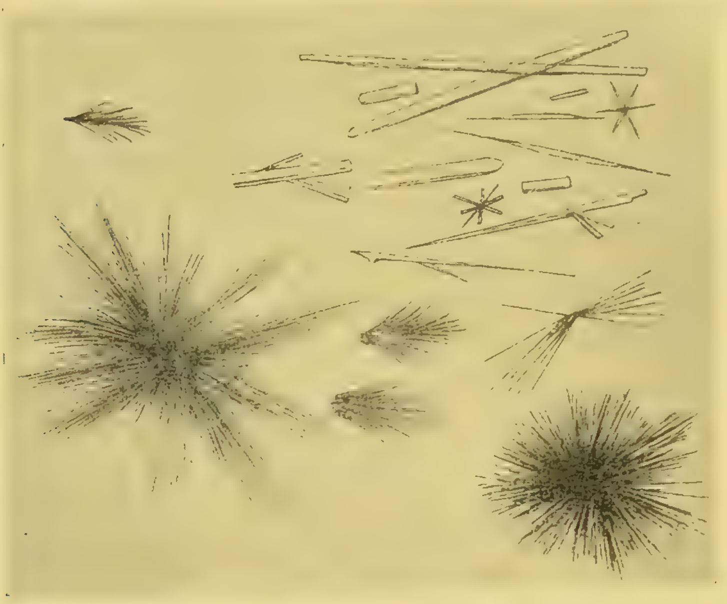


FIG. 13.—Tyrosine crystals. (Halliburton, *after* Frey.)

TEST FOR TRYPTOPHANE, OR INDOLE-AMINO-PROPIONIC ACID.

Add a little bromine water; this produces a violet colour. If a little amyl alcohol is then added, and the mixture gently shaken and then allowed to stand, the alcohol rises to the top and contains the violet pigment in solution.

TEST FOR INDOLE.

Cholera-red reaction:—Add a little sulphuric acid and a few drops of a dilute solution of sodium nitrite: a bright red colour appears.

2. **Upon Fat.**—Before fat can be readily split into glycerin and fatty acid it must be emulsified—that is to say, broken up into very fine globules such as are present in milk.

Emulsification.—The process of emulsification is a physical one, and is brought about in the small intestine by means of various agencies. These are as follows:—

(*a*) The movement and warmth of the intestines.

(*b*) The presence of mucin and nucleo-proteins. These are viscid substances, and viscidity aids the process.

(*c*) The alkalinity of the intestinal contents. Pancreatic juice is definitely alkaline, and fresh bile is faintly alkaline.

Saponification.—The emulsified fat is further chemically split, by the action of pancreatic lipase, into glycerin and fatty acid. Triolein is split into glycerin and oleic acid; tripalmatin is split into glycerin and palmitic acid, and tristearin is split into glycerin and stearic acid. Pancreatic lipase also splits the lipoid lecithin into glycero-phosphoric acid, stearic acid, and choline, the last being a poisonous alkaloid. The choline is further broken up by the bacteria, which are present in the intestine, into such inert bodies as carbon-dioxide, marsh gas, and ammonia. Some of the fatty acids unite with the alkaline bases present to form a soluble soap.

3. **Upon Carbohydrates.**—The pancreatic juice of the young infant has no action upon carbohydrates, because it contains no amylolytic enzyme; hence babies are unable to digest starch. The pancreatic juice of the adult, however, contains a very active amylolytic enzyme, amylopsin, which is capable of acting upon uncooked as well as cooked starch, and converting these into soluble starch; this is further split into erythro-dextrin and achroö-dextrin, the final products being achroö-dextrin and maltose.

The pancreatic is the most active of the digestive juices. Trypsin is a more powerful catalyst than pepsin, and amylopsin is a more powerful catalyst than ptyalin,—in other words, the velocity of reaction is greater in the case of trypsin and amylopsin than it is in the case of pepsin and ptyalin.

As trypsin is such a powerful enzyme, the question naturally arises, why is it that the pancreatic juice does not digest the pancreas itself? The pancreatic juice as it occurs in the ducts of the pancreas contains the inactive trypsinogen, and it is not until the juice leaves the ducts of Wirsung and of Santorini, and gets into the lumen of the intestine, that it meets the activator enterokinase, which converts the inactive trypsinogen into active trypsin.

CHAPTER XII.

SUCCUS ENTERICUS.

The mucous membrane of the intestine contains innumerable simple, straight, tubular glands, which are lined by flattened columnar cells supported on a basement membrane. These are Lieberkühn's crypts, and are plentifully supplied with blood and secrete the succus entericus. Although it is somewhat difficult to obtain succus entericus in any appreciable amount, it will be understood that the twenty feet of small intestine must secrete a large quantity of intestinal juice.

METHODS OF OBTAINING SUCCUS ENTERICUS.

Vella's Method.—A few inches of the small intestine of a dog are severed from the main portion, care being taken that the blood-vessels and nerves supplied to this isolated piece are undamaged, and the two ends of this part are sutured to the abdominal parietes. Two intestinal fistulæ are thus produced, and from these openings succus entericus may be obtained. It is obvious that the two cut ends of the gut must be accurately sutured one to the other, and returned to the abdomen so that digestion may go on in the usual manner.

Thiry's Method.—This is similar to Vella's, except that one end of the isolated loop of small intestine is sewn up, and the free end is sutured to the abdominal wall; and from this tube, closed at one end, succus entericus may be obtained.

CHARACTERS OF SUCCUS ENTERICUS.

It is a yellowish opalescent alkaline fluid having a specific gravity of about 1010. It contains alkaline salts, chiefly sodium carbonate, an activator called zymolysin, or enterokinase; certain enzymes, such as invertase, lactase, maltase;

and an enzyme, which has some slight action upon starch, also a proteolytic enzyme, erypsin.

THE ACTION OF SUCCUS ENTERICUS.

1. **On Carbohydrates.**—Succus entericus has a slight action upon starch, converting it into dextrin, and finally into sugar. By virtue of the enzyme, invertase or sucrase, cane sugar, which is dextro-rotatory, is converted into dextrose and lævulose. The lævo-rotatory power of the lævulose is greater than the dextro-rotatory power of the dextrose; hence this is an example of *inversion*, an enzyme converting a dextro-rotatory sugar into a mixture which is lævo-rotatory. By the action of the lactase, milk sugar or lactose is converted into dextrose and galactose. And by the action of the maltase, maltose is converted into dextrose.

Cane sugar . invertase = Dextrose and lævulose.
Lactose . lactase = Dextrose and galactose.
Maltose . maltase = Dextrose and dextrose.
$C_{12}H_{22}O_{11} + H_2O = C_6H_{12}O_6 + C_6H_{12}O_6$.

2. **On Proteins.**—By the action of the enzyme, erepsin, which is actively proteolytic or proteoclastic, proteoses, peptones, protamines, histones, and polypeptides are finally split into monoamino-acids, diamino-acids, aromatic amino-acids, and ammonium compounds. Although it should be noted that erepsin has no action upon native protein such as egg-albumin, egg-globulin, and fibrin. The chief protein of milk, however, calcium caseinogenate, is split by erepsin into simpler substances. The action of erepsin, therefore, is all-important in infants, in whose alimentary canal pepsin and trypsin are either absent or present only in very small quantities.

Vines has shown that an enzyme of the nature of erepsin is present in certain carnivorous plants, and Vernon states that enzymes of the nature of erepsin are generally present in most animal tissues, especially in the kidney. It has already been stated that succus entericus contains a substance called zymolysin or enterokinase (ferment of ferments), which is essentially an activator, the function of which is to convert the inactive trypsinogen into active trypsin. At the same time, enterokinase is said to be capable of activating pancreatic lipase.

CHAPTER XIII.

THE LIVER.

GENERAL STRUCTURE OF THE LIVER.

The liver is essentially a lobular organ, the lobules of which may more readily be seen in the liver of some of the lower animals. The larger portion of the liver is covered over by the peritoneum, beneath which is some fine areolar tissue called Glisson's capsule, which extends into the liver substance through the portal fissure, and surrounds the portal systems, which include a branch of the portal vein, a branch of the hepatic artery, and a bile duct. Each lobule is about 1 mm. in diameter, and consists of a number of polyhedral cells loosely packed, together with a particular arrangement of blood vessels and bile capillaries.

The arrangement of the blood vessels and bile capillaries is as follows :—

The portal vein brings back the blood from the spleen, stomach, duodenum, pancreas, small intestine, and the greater part of the large intestine to the liver. The portal vein has a relatively large amount of plain muscle in its walls, to which vasomotor nerves are distributed. After entering the transverse fissure of the liver, the portal vein divides into right and left branches for the right and left lobes respectively ; each branch breaks up into veins which run between the liver lobules. These are the *interlobular* veins, which give off the lobular blood capillaries, which form a fine network within the lobule itself. These capillaries open into sinusoids between the liver cells, and, for the most part, the protoplasm of the liver cells forms the wall of the sinusoids. It is said that some of the blood plasma in these sinusoids gets into minute *intracellular* canals situated within the liver cells (Schäfer), so that in this way the liver cell is brought into intimate relationship with the fluid in the sinusoids derived from the portal vein. The intracellular blood canals are too minute to admit the blood corpuscles; they simply transmit the plasma.

The sinusoids converge towards a vein, the *intralobular* vein, in the centre of the liver lobule, which is the commencement of the hepatic system of veins. The intralobular veins open out into the sublobular veins, which converge to form the hepatic vein. The hepatic veins open into the inferior vena cava. It will be seen that the blood, which reaches the liver through the portal vein, is brought into intimate relationship with the cells in the liver lobules. The hepatic artery breaks up in a similar manner to supply the right and left lobes of the liver. Each branch divides between the liver lobules as the interlobular arteries, which give off minute capillaries running into the liver lobule, and ending in the middle zone of the lobule by opening into the sinusoids derived from the portal vein. In this way the hepatic vein takes back from the liver blood brought to it by the portal vein and the hepatic artery. The bile capillaries commence in intracellular bile vacuoles, which exist within the protoplasm of the liver cell, and in this way the protoplasm of the liver cells can readily excrete material into the bile capillaries. The intracellular bile vacuoles open into minute intracellular bile capillaries, which run outwards from the liver cells and join with neighbouring intracellular bile capillaries to form the intercellular bile capillaries. These run between the liver cells,—in fact, where they first form, their walls consist of the protoplasm of the liver cells themselves. These bile capillaries traverse the liver lobule as the lobular bile capillaries, and then open into interlobular bile canals, which are lined by columnar epithelial cells supported on a basement membrane; these are the small bile ducts. The intracellular bile vacuoles and canaliculi may be demonstrated by one of the following methods:—

(1) Inject into the jugular vein of a dog a saturated watery solution of sodium sulph-indigotate (blue), and allow it to circulate for one hour and a half, then kill the animal and wash the blood vessels quite free from blood. If the liver is examined, blue pigment will be found in the liver cells, in the bile canaliculi, and in the bile ducts. (2) Stain fresh liver by Golgi's silver-chrome method, the intracellular bile vacuoles and canaliculi will become black.

THE STRUCTURE OF LIVER CELLS.

If a piece of fresh liver is teased in a normal saline solution the liver cells are seen to be somewhat ovoid in shape, but when they are packed in the liver lobules they appear to be polyhedral, with spaces between for the blood to traverse the intercellular capillaries and sinusoids, and for the bile to traverse the intercellular bile canaliculi. Each liver cell has a central oval nucleus. In the protoplasm of the cell the intracellular blood capillary, the intracellular bile vacuole, and canaliculus may be demonstrated. In the protoplasm are numerous granules, some of which are protein granules, which can be fixed brown with osmic acid; and some are fat globules, which may be demonstrated by the fact that the triolein present reduces osmic acid to a lower oxide of osmium, which is black, and granules consisting of iron in organic combination, which may be demonstrated by the fact that they become blue when the liver is treated with ferrocyanide of potassium and a little acetic acid. The iron becomes black when the fresh liver is hardened in alcohol containing ammonium sulphide in solution, the black sulphide of iron being produced in the liver cells. Some of the granules found in the liver cells are no doubt pigment granules. Clear material may also be seen in the protoplasm of the liver cell, which stains a brownish-red colour with a solution of iodine. This clear material is glycogen.

THE FUNCTIONS OF THE LIVER.

These may be briefly stated as follows :—

1. **Glycogenic Function.**—The liver cells are supplied by the glucoses—dextrose, lævulose, and galactose—which are absorbed from the intestine; and the liver cells, possibly activated by the internal secretion of the pancreas, store up animal starch or glycogen $(C_6H_{10}O_5)_n$; and, according to Claude Bernard's theory, the glycogen so stored by the liver cells is gradually, by an endo-cellular enzyme, converted into dextrose, and the dextrose thus produced leaves the liver by the hepatic vein, and so is distributed to the tissues of the body for further use. According to Pavy's view, the glycogen so stored up in the liver cells is never re-converted into carbohydrate, but is on the way to *help* to form fat and protein in the tissues. It is true that a rich carbohydrate diet increases

the deposition of fat in the fat depôts of the body, and also that many tissue proteins contain a carbohydrate radical. The glycogenic function of the liver is under the control of the central nervous system. The centre seems to be in the upper part of the medulla, bounded above by the roots of the auditory nerve and below by the vagus nucleus. Puncture of this region *irritates* the nerve cells of the centre, and is followed by increased production of dextrose from the stored glycogen, hyperglycæmia, and glycosuria of short duration. The centre may be reflexly excited by stimulation of the upper cut end of certain afferent nerves, *i.e.* the vagi, the depressor, or any large mixed nerve such as the sciatic. The efferent path for the impulses seems to be down the spinal cord to the upper dorsal region, through the anterior nerve roots into the white rami communicantes, thence through the lower cervical and upper thoracic sympathetic ganglia, and by the splanchnic nerves to the liver. Macleod says : "As to the exact nature of the glycosuria-producing impulses we know very little. They may be merely vasomotor, and cause dilatation of the hepatic vessels, by means of which an increased sugar production is induced (Bernard); or it may be that there are in the splanchnics true secretory fibres concerned in the control of the enzyme production in the hepatic cells. Pflüger offers an ingenious speculation regarding the rôle in the animal economy of the reflex control of sugar production in the liver. Sugar is the most available food stuff for muscular contraction, so that when a muscle contracts it uses up some sugar; at the same time, however, by compression of the muscle spindles, afferent nervous impulses are set up which are carried up to the 'diabetic centre,' and so lead to the formation of more sugar from the liver. The heart is the most active muscle in the body, and consequently requires most sugar; its afferent fibres to the 'diabetic centre'—carried by the vagus—are therefore the most active of all" (*vide* p. 384).

Preparation of Glycogen from the Liver.—A rabbit which has been previously fed on carrots is killed, the abdomen and thorax then rapidly opened, and the liver exposed. A cannula is fixed in the portal vein, and another in the inferior vena cava in the thorax. The liver is then perfused with a normal saline solution through a cannula in the portal vein, and the washings as they leave the liver may be collected from the cannula in the inferior vena cava. The early washings from the liver contain sugar, the intermediate washings less sugar, and the last washings may contain no sugar. In this way the blood of the liver and the contained sugar must be carefully washed out. It may be seen that the liver washing is successful, because it loses its bright red colour, becomes pale and swollen by the salt solution which distends its vessels. When the liver is thoroughly washed through it is rapidly removed, the gall bladder excised, and the liver cut into small pieces. These are then thrown into boiling water previously acidulated with a little acetic acid. This coagulates the proteins and kills the enzymes which are present, at the same time the water abstracts some of the glycogen. The scalded liver is then placed in a mortar and some finely powdered sand or glass and boiling water are added. The whole is carefully ground up, and further extracted with boiling water. On filtering, the extracted glycogen goes through the filter, whereas the coagulated protein, the fat, the connective tissue, and the powdered glass remain on top of the filter. The greenish opalescent filtrate is now slowly evaporated to concentration, and the glycogen precipitated from it by adding alcohol until the amount of it present is about 55 per cent. The glycogen may then be dried. It is a white, tasteless, amorphous powder, soluble in cold water, producing an opalescent solution. On adding to a solution of glycogen a drop or two of iodine solution a reddish-brown colour is produced, which disappears on warming and reappears on cooling. Glycogen may be precipitated from its solution by adding a few drops of basic lead acetate. It is also precipitated by saturation with ammonium sulphate crystals.

2. **Urea Formation.**—The greater part of the urea produced in the body is formed in the liver (*vide* p. 360). The liver cells form the urea from two sources :—

(1) The larger amount, produced by the liver cells, is derived from the amino-acids which have been absorbed from the small intestine, and which are not required by the tissues ; this constitutes the *exogenous urea.*

(2) The smaller amount, produced by the liver cells, is derived from the ammonium carbonate, which is the outcome of nitrogenous katabolism, and which is derived from the tissues ; some is also produced by the action of the uricolytic enzyme upon uric acid ; this constitutes the *endogenous urea.*

3. **Uric Acid Formation.**—Uric acid is formed in the liver

more abundantly than in other tissues. It is the result of the complete oxidation of certain purine bases, which are derived partly from the nucleo-protein in the tissue (*endogenous uric acid*), and partly from the nucleo-protein of the food (*exogenous uric acid*). Much of the uric acid thus formed is further changed by the uricoclastic or uricolytic enzyme, produced by the liver cells, into urea (*vide* p. 371).

4. **The Formation of Creatinine** ($C_4H_7N_3O$).—Creatinine is formed in the liver from substances of unknown composition carried to it by the blood stream. The creatinine so formed is carried to the muscles of the body, where it is stored as creatine (*vide* p. 366).

5. **Bile Formation.**—The liver may be considered as an extremely important filter, excreting into the bile certain waste products, the result of katabolic changes which take place in the tissues and the liver itself. It is also probable that the liver gets rid of, or neutralises, many poisonous substances, which have entered the intestinal wall from the alimentary canal, and in this way it may be considered as an organ which safeguards the tissues from such poisons. How the liver cells act in this way is not known; there are, however, two chief possibilities. One is that the liver cells secrete anti-bodies which neutralise the effect of these various poisons arriving by the portal blood. The other is that the liver cells secrete oxidases, which oxidise toxic substances into inert compounds. There are also reasons for believing that the liver not only filters off bacteria, which arrive by the portal vein, but that it also aids in their destruction (Batty Shaw). If more poisons are produced in the tissues, or absorbed from the alimentary canal, than the liver is capable of dealing with, or if the liver cells are so destroyed that they cannot deal with such poisons, then the symptoms of toxæmia arise. Most of these waste substances, which are eliminated by the liver, help to form the bile, and as bile they escape again into the intestine, to be excreted for the most part in the fæces.

6. **A Blood Reservoir.**—The liver, which contains a very large vascular area, may be considered as a reservoir for blood on its way to the heart, and so to a certain extent it helps to prevent the right side of the heart from becoming over distended.[1] This fact may be demonstrated experimentally. It

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[1] In much the same way the lungs act as reservoirs for the left side of the heart, and help to prevent its over-distension.

is found that, if a solution of proteose is injected into the blood stream of an animal, and certain organs such as the kidney, spleen, liver, and even a limb are put into a plethysmograph, the general result is vasodilatation and a consequent enlargement of the various organs, due to engorgement of the blood capillaries. It is found, however, that the liver becomes relatively much larger than the other organs, and this seems to point to the fact that the liver accommodates a large amount of the blood on its way to the heart. This reservoir action of the liver is also observed clinically. In chronic cardiac disease, when broken cardiac compensation occurs and the signs of back pressure set in, that is, when the arteries become under filled and the veins over filled, the liver is the first organ to become enlarged. The intralobular veins become passively congested, the neighbouring liver cells undergo fatty degeneration, and the condition known as nutmeg liver is produced.

7. **Production of Anti-thrombin.**—It is believed that the liver cells secrete anti-thrombin, a substance which neutralises the action of the circulating thrombin, or fibrin enzyme, and in this way intravascular coagulation is prevented. When, in abnormal circumstances, thrombosis, or blood clotting, does take place in the body, it may be due either to too much thrombin or fibrin enzyme being liberated, or to too little anti-thrombin being secreted by the liver cells.

8. **Erythrocytes.**—A large amount of the arterial blood which leaves the placenta travels straight back to the liver of the fœtus by the umbilical vein and the venæ advehentes, and it is believed that red blood corpuscles of the fœtus are formed in its liver. In the adult, however, the useless red blood corpuscles are finally chemically disintegrated, and the iron of the hæmoglobin in organic combination is deposited in the liver cells. This is gradually removed, possibly by the white blood corpuscles, and utilised over again in the red marrow of bone to form new hæmoglobin. In the disease known as primary, or idiopathic, pernicious anæmia, in which there is an increased hæmolysis, or destruction of red blood corpuscles, taking place in the body, there is an increased deposit of iron in organic combination in the middle and outer zones of the liver lobules.

9. **Heat Production.**—From these statements it will be seen that metabolic changes take place to a very marked extent in the liver, and that in this way the liver participates with the

muscles, and some of the other glands in the body, in being an organ in which oxidation takes place somewhat rapidly. It may therefore be looked upon, at any rate, as one source of animal heat (*vide* p. 414).

BILE.

For ordinary examination, bile is usually obtained from the gall-bladder post-mortem, but it may be obtained during life from a biliary fistula,—that is, an opening made between the gall-bladder and the skin of the animal. If the animal is fed in the usual way, it is found that there is an early flow of bile from the gall-bladder, no doubt due to the fact that some acid gastric chyme leaves the stomach and gets into the duodenum, the hydrochloric acid being the chemical excitor. Following this there is a later flow of bile, due to the absorption of secretin, which stimulates the liver cells to secrete bile, just as it stimulates the cells of the pancreas to secrete the pancreatic juice. It has been found experimentally that the secretion of bile is much quickened by the injection of secretin into the blood stream.[1] Bile is secreted at a pressure varying from 15 to 30 mm. Hg., the pressure of the blood in the portal vein is roughly 10 mm. Hg., so that, when obstruction takes place to the outflow of bile along the ductus communis choledochus, bile readily passes into the lymph stream, thence to the thoracic duct and blood stream, and the individual becomes jaundiced; following this the bile pigments and bile salts are excreted in the urine.

The amount of bile secreted daily varies from 500 to 1000 c.c.

Composition of Bile.—The bile of herbivorous animals is, as a rule, dark green, that of carnivorous animals is orange-red. In man the colour is yellowish-green. Fresh bile is transparent and viscid; this viscidity is due to the presence of nucleo-protein in ox bile and to mucin in human bile. Bile is extremely bitter; it has an aromatic odour, and its reaction is just alkaline; the specific gravity varies from 1010 to 1011 (fistula bile), 1026–1030 (gall-bladder bile).

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[1] Bile, which is secreted by the liver cells, passes into the bile ducts down the common hepatic duct, and much of it is stored in the gall-bladder. It is expelled from the gall-bladder by the contraction of the muscle in its walls. Cholagogues (bile drivers) act in two ways: (1) By causing more rapid movements of the contents of the intestines, so that sufficient time is not allowed for the absorption of bile salts; (2) by causing the contraction of the muscular wall of the gall-bladder.

Bile from the gall-bladder consists of:—

Water	85 per cent.
Solids	15 ,,
Bile salts (sodium taurocholate and sodium glycocholate)	10 ,,
Mucin or nucleo-protein Bile pigments (bilirubin and biliverdin)	3 ,,
The lipoids, cholesterin, and lecithin together with neutral fats, about	1·5 ,,
Inorganic salts, chiefly sodium chloride, potassium chloride, calcium phosphate, magnesium phosphate, and a trace of iron phosphate; these together form about	0·7 ,,

Bile contains also a certain amount of carbon-dioxide. The tension of the CO_2 in bile is greater than the tension of it in the venous blood from the liver; this suggests that the liver cells are capable of secreting the gas.

The Bile Salts.—The bile salts are sodium glycocholate and sodium taurocholate. These may be separated from the bile as follows:—

1. Evaporate the bile to a quarter of its bulk in order to concentrate.

2. Add to the concentrated bile powdered animal charcoal, and rub to a paste. The animal charcoal absorbs the colouring matter.

3. Add to the mass alcohol; this dissolves out the bile salts.

4. Add to the alcoholic extract neutral lead acetate; this forms a precipitate of lead glycocholate.

5. The lead glycocholate is dissolved in hot alcohol, and H_2S gas passed through the solution. This precipitates the lead as lead sulphide, and glycocholic acid remains in solution.

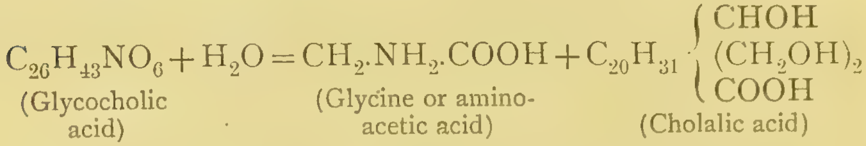
6. After the lead glycocholate has been precipitated and removed, the taurocholate may be precipitated by adding basic lead acetate and ammonia.

Sodium glycocholate is more abundant in the bile of herbivorous animals and man; sodium taurocholate is more abundant in carnivorous animals.

Glycocholic acid may be prepared from bile as follows:—

Ten c.c. of ether are added to 100 c.c. of fresh ox bile and the mixture is well shaken. Four c.c. of concentrated hydrochloric acid are then added, and the mixture is further well shaken. On standing, glycocholic acid separates out.

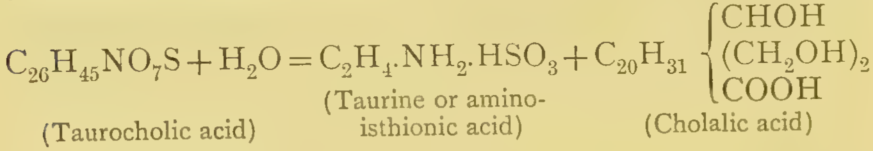
Glycocholic acid ($C_{26}H_{43}NO_6$), when it gets into the intestine, is there broken up into glycine ($CH_2.NH_2.COOH$) and cholalic acid [$C_{20}H_{31}CHOH(CH_2OH)_2COOH$]. A similar decomposition may be brought about by the action of weak alkalies and weak acids.



$$\underset{\text{(Glycocholic acid)}}{C_{26}H_{43}NO_6} + H_2O = \underset{\text{(Glycine or amino-acetic acid)}}{CH_2.NH_2.COOH} + \underset{\text{(Cholalic acid)}}{C_{20}H_{31}\left\{\begin{array}{l}CHOH\\(CH_2OH)_2\\COOH\end{array}\right.}$$

Glycocholic acid is soluble in hot water and in alcohol; it is slightly soluble in ether. Glycine is a normal product of proteolysis.

Taurocholic acid ($C_{26}H_{45}NO_7S$) in the intestine is broken up into taurine or amino-isthionic acid ($C_2H_4.NH_2.HSO_3$) and cholalic acid. It may also be decomposed, by boiling with weak alkalies or weak acids or with barium hydrate, into taurine and cholalic acid.



$$\underset{\text{(Taurocholic acid)}}{C_{26}H_{45}NO_7S} + H_2O = \underset{\text{(Taurine or amino-isthionic acid)}}{C_2H_4.NH_2.HSO_3} + \underset{\text{(Cholalic acid)}}{C_{20}H_{31}\left\{\begin{array}{l}CHOH\\(CH_2OH)_2\\COOH\end{array}\right.}$$

Taurine has been formed artificially from cystine, a normal constituent of proteins. Cholalic acid may be broken up, by putrefaction and by the action of acids, into an insoluble hydride called dyslysin.

The Origin of Bile Salts.—Bile salts are produced by the liver cells. Their immediate precursors are most probably some of the tissue proteins, including hæmoglobin; for there is no doubt that the sulphur contained in hæmoglobin and other proteins is eliminated in the taurocholic acid. In the bile the salts are excreted into the intestine, but Schiff has shown that bile salts circulate, which means that a certain proportion is reabsorbed. In the intestine, fat is split into glycerin and insoluble fatty acid; this latter is soluble in bile salts, and in this way is absorbed with the bile salts, which get to the liver by the portal vein, to be excreted once again (Schiff's circulation of bile salts). On the other hand, some of the bile salts are split in the intestines into glycine, taurine, and cholalic acid, and some of these substances are absorbed as well. Some of the glycine may be converted in the liver into urea, some of the taurine into organic sulphates, which are found in the urine.

TESTS FOR BILE SALTS.—*Pettenkofer's Test.*—This test depends upon the presence of cholalic acid. Into a white capsule is put a trace of bile, a small quantity of a solution of cane sugar, and a little concentrated sulphuric acid; after the mixture is gently warmed a brilliant purple colour is produced. This is due to the fact that the sulphuric acid acts upon the cane sugar, producing, amongst other substances, furfurol or furfuraldehyde, which in the presence of cholalic acid gives a purple colour. This test may be performed in a test tube; when the bile and the cane sugar are shaken together a froth is produced on the top, a drop of concentrated sulphuric acid is poured through the froth, the purple colour appears in the froth, especially on being warmed.

Hay's Test.—Pettenkofer's test cannot be obtained in urine if the bile salts are present in small quantity only. But if a light powder, flowers of sulphur, is placed upon the top of urine, which contains a trace of bile salts, the powder will gradually sink. This is due to the fact that bile salts in solution diminish the surface tension and allow the fine particles of the powder to fall through the fluid. Flowers of sulphur will not sink in normal urine.

Bile Pigments.—Human bile contains bilirubin ($C_{16}H_{18}N_2O_3$) and biliverdin ($C_{16}H_{18}N_2O_4$). Bilirubin is more abundant in the bile of carnivora, and biliverdin in that of herbivora. Biliverdin is an oxidation product of bilirubin. Bile pigments show no absorption bands with the spectroscope. Either pigment, however, may be reduced, when dissolved in dilute potash, by sodium amalgam with the formation of hydrobilirubin ($C_{32}H_{44}N_4O_7$), which gives two absorption bands, one near the D line and one near the F line of the spectrum. Hydrobilirubin is allied to stercobilin, the pigment of the fæces, and to urobilin, one of the pigments of the urine. These, stercobilin and urobilin, are probably the same substance. Bilirubin is identical with hæmatoidin, an iron-free derivative of hæmoglobin, which is found in the body in the neighbourhood of old hæmorrhages, especially in the brain and lung (hæmorrhagic infarct). Hæmatoidin forms definite dark red crystals, and gives no absorption bands in the spectrum.

GMELIN'S TEST FOR BILE PIGMENTS.—If a drop of fuming nitric acid (nitric with nitrous acid) is added to a little bile in a white capsule, a play of colours is produced; this is due to oxidation products. The bilirubin is oxidised to biliverdin (green), then to bilicyanin (blue), then to bilipurpurin (violet and red mixed), and the final product is choletelin (yellow) ($C_{16}H_{18}N_2O_6$).

The Origin of Bile Pigments.—The bile pigments are formed by the liver cells from the disused hæmoglobin which is derived from the disintegrated red blood corpuscles. The elements carbon, hydrogen, oxygen, and nitrogen of the hæmoglobin occur in the bile pigments; the sulphur of the hæmoglobin is eliminated in the sodium taurocholate. The iron of the hæmoglobin is deposited in the liver cells, to be used over again in the red marrow of bone to help to build up more hæmoglobin, which is carried away in the newly formed coloured corpuscles.

Cholesterin or **Cholesterol** ($C_{27}H_{45}OH$).—Cholesterin is a lipoid which is found abundantly in the fatty sheath of the nerves, and therefore is in greatest quantity in the brain and spinal cord, from which it can be readily obtained. Rosenheim has introduced the following method for obtaining cholesterin from the brain. The crushed brain is mixed with plaster of Paris in order to extract all the water. The cholesterin is extracted with acetone, which extracts nothing else. The acetone is distilled off and cholesterin remains. Cholesterin is also found in both the coloured and colourless blood corpuscles, and in lymphoid tissue. It is probably being excreted in the bile. Occasionally it is precipitated in the gall-bladder and hepatic ducts in the form of cholesterin gall-stones, and is sometimes precipitated with bilirubin calcium; it helps to form the mixed gall-stones, and is also found in the fæces. Cholesterin is a terpene,—that is, an aromatic substance with five reduced benzene rings linked together; pure cholesterin is lævo-rotatory (*vide* p. 49).

TESTS FOR CHOLESTERIN.—1. It is crystalline, and forms flat colourless crystals, often appearing to have a corner notched out.

2. If a few cholesterin crystals are placed on a slide, and a little concentrated sulphuric acid and a trace of water added,

and the slide gently warmed, the margins of the crystals turn red, and the crystals soon lose their crystalline form.

3. *Salkowski's Test.*—Into a *dry* test tube is placed a little concentrated sulphuric acid, and cholesterin, previously dissolved in chloroform, is gently run on to the acid. Where the acid comes in contact with the chloroform solution of cholesterin a bright cherry-red ring is produced. The red colour diffuses through the chloroform solution, and the subjacent sulphuric acid acquires a greenish fluorescence, best seen on a black background.

4. *Liebermann's Test.*—To a chloroform solution of cholesterin, placed in a *dry* test tube, a few drops of acetic anhydride (undiluted) are added, then two or three drops of concentrated sulphuric acid, and the mixture gently shaken. First a purple colour is produced, which gradually becomes blue, followed by a greenish tint.

Functions of the Bile.—Although the bile is chiefly excretory in function, yet it certainly has some secretory action. Its functions may be mentioned under the four following headings:—

1. ITS DIGESTIVE ACTION.—(*a*) *On Protein.*—Bile salts in the presence of a weak acid precipitate unpeptonised protein, such as proteose. This action may be shown by adding bile to a solution of proteose which contains a little hydrochloric acid. In this way it is believed that the bile precipitates unpeptonised protein contained in the acid gastric chyme which arrives in the duodenum, and causes it to be caught by the valvulæ conniventes. It is then further digested by the trypsin-sodium-carbonate of the pancreatic juice. In other words, bile aids the pancreatic juice in digesting protein.

(*b*) *On Fats.*—Bile, through its viscidity and the presence of bile salts, aids in emulsifying fat, and so prepares the fat for the action of the pancreatic lipase.

(*c*) *On Carbohydrates.*—It is found experimentally that pancreatic juice in the presence of bile splits starch into achroödextrin and maltose more readily than pancreatic juice acting alone does. In this way it is probable that bile aids pancreatic juice in digesting starch. In some herbivorous animals the bile contains an enzyme which has some slight amylolytic action.

2. BILE AIDS THE ABSORPTION OF FAT.—This occurs in the villi of the small intestine.

The columnar cells on the surface of the villi, being bathed in bile, have their surface tension somewhat diminished, so that particles of material may pass through them more easily. Fatty acid is insoluble in water, but is soluble in bile salts, and it is probable that some of the fatty acid which is absorbed goes through the columnar cells over the villi accompanied by bile salts. When bile is absent from the intestine, such as occurs through obstruction to the common bile duct, undigested and unabsorbed fat may be obtained from the fæces.

3. It has been stated that bile itself is mainly *excretory*, since by its means certain waste products are eliminated, but bile itself has some stimulating action upon the coats of the intestine, and therefore, to a certain extent, it helps to produce peristaltic movements. It may therefore be looked upon as the *natural laxative*. It should be noted that one of the early signs of jaundice, due to obstruction of the common bile duct, is constipation.

4. Bile in the intestine, to some extent, *limits putrefactive changes*, and in this way renders the fæces less offensive. If bile is not excreted into the intestine, putrefaction goes on to a more advanced stage than in normal circumstances; after a time the poisonous substances produced irritate the wall of the large intestine, and offensive diarrhœa results.

THE LARGE INTESTINE.

The mucous membrane of the large intestine is lined by simple straight tubular glands, which are closely set together. For the most part the cells near the mouths of these glands are mucous-producing or goblet cells. Beneath the simple tubular glands there is much lymphoid tissue. The mucous membrane of the large intestine is alkaline in reaction, though the contents are usually acid due to acids of fermentation and also to fatty acids,—in fact, the reaction of the intestinal contents, quite high up in the small intestine, may be acid: this is due to the presence of fatty acids. In the lumen of the intestine bacteria abound; they produce enzymes which are capable of splitting proteins into peptones, polypeptides, and amino-acids; starch into sugar; and fats into glycerin and fatty acids. In the large intestine putrefactive changes due to bacterial action go on extensively; the chief bacterium present is the *Bacillus coli.* Some of the tyrosine and tryptophane, produced by the action of trypsin and erepsin, are broken up into aromatic substances such as indole, skatole, and phenol. From some of the fats, fatty acids, such as valeric and butyric, are produced. Some of the lactose undergoes lactic acid fermentation, cellulose is broken up into CO_2,H_2, and CH_4. Poisonous substances like choline, derived from lecithin, are broken up into CO_2, CH_4, and NH_3. Proteins give rise to H_2S. There is some free N present in the colon.

CHAPTER XIV.

ABSORPTION.

The whole purpose of digestion is to break up large molecules of material into much smaller molecules, in order that they may pass through the wall of the intestine, get into the blood and the lymph stream, and thus be carried to the tissues, where constructive metabolism or assimilation takes place. None of the products of digestion are absorbed in the buccal cavity, pharynx, or œsophagus, and in normal circumstances practically no absorption takes place from the wall of the stomach, not even water. On the contrary, however, alcohol is readily absorbed from the stomach, and this, to a great extent, explains the rapidity with which it produces its effects. The greater part of the digested food is absorbed by the villi which exist over the valvulæ conniventes which are present in the small intestine.

THE STRUCTURE OF A VILLUS.

The villi are finger-shaped processes which give the mucous membrane of the small intestine its velvety appearance. On the surface of the villus is a single layer of columnar epithelial cells, the free border of which is longitudinally striated. The protoplasm is granular. The larger granules near the base of the cells stain black with osmic acid and are presumably fat. Some of the columnar cells near the apex of the villus are goblet cells which secrete mucin. Between the columnar cells, near their bases, small cuboidal or spheroidal cells are wedged, and between the columnar cells are lymphocytes. In the centre of the villus is the lacteal radical, the free extremity of which is somewhat bulbous. This is lined by an endothelium. Between this endothelial wall of the central lacteal and the columnar cells on the surface is lymphoid tissue, which consists of triangular branching cells which form a network in the meshes of which are found the lymphocytes. Around the central lacteal are strands of plain muscle fibres, the function of which is to contract and squeeze out the contents of the central lacteal towards the general lacteal stream. Just beneath the bases of the columnar cells are the minute capillaries which form the portal vein radicals. Breaking up around the central lacteal are the capillaries derived from the arterioles which ramify in the submucous tissue. The nerves to the villi are derived from Meissner's plexus, which is present in the submucous coat of the intestine.

As the result of the digestive processes which go on in the alimentary canal, proteins are broken up into amino-acids, fat is split into glycerin and fatty acid, the latter is dissolved by the bile salts which are in solution. Some of the fatty acid combines with the alkali present to form a soluble soap. The carbohydrates are converted into the glucoses—dextrose, lævulose, and galactose. The salts taken with the food are unaltered during digestion.

The function of the villi is to absorb these products of digestion, and this is brought about mainly by the biotic activity of the columnar striated cells on the free surface of the villi. Absorption of the products of digestion depends upon two chief factors :—

1. The physical. 2. The physiological.

The physical factors depend chiefly on the processes of diffusion and osmosis. The salts which are in solution in the water ionise, and substances, such as NaCl, break up into soda ions, and chlorine ions. If the soda ions (kations) predominate they may depress the activity of the columnar cells, but if the chlorine ions (anions) predominate it is believed that the salt stimulates the columnar cells to increased activity. In this way the absorption of water and dissolved salts, and possibly the absorption of the products of digestion, may be accounted for. But, after all, the main absorptive process depends upon the biotic activity of the columnar cells. It has been shown by Weymouth Reid that, if a solution of sodium fluoride is administered to an animal, it poisons the majority of the columnar cells, many of them exfoliate, and absorption no longer takes place. Moreover, if some of an animal's own blood serum is introduced into an isolated loop of small intestine it is absorbed, although it has the same osmotic pressure as the animal's blood. This experiment proves that absorption depends, to a very considerable extent, upon the biotic activity of the cells over the villi. It has been found that the micro-organisms of cholera, which get into the intestine, produce coagulation necrosis, or death of the columnar cells over the villi; these cells then exfoliate, and absorption no longer takes place. During absorption there is a digestive lymphocytosis in the blood, that is, an increase in the number of lymphocytes, and it has been suggested that these cells help in carrying absorbed materials from one tissue to another.

THE ABSORPTION OF PROTEIN.

The view previously held with regard to the absorption of protein was that during digestion protein was finally converted into peptone, and the peptone so produced was absorbed by the columnar cells over the villi, and built up again by these cells into serum albumin and serum globulin, the chief proteins of the blood plasma. The view generally accepted now is that protein is completely hydrolysed into the cleavage products (Bausteine or "building stones") known as amino-acids in the intestine; and it is these amino-acids which, being smaller molecules than the original protein, readily pass through the striated free border of the columnar cells over the villi and so get into the protoplasm of these cells. Here a synthesis takes place, and some simple and aromatic amino-acids are converted by the columnar cells into serum albumin and serum globulin, the native blood proteins and this protein is conveyed to the tissues. On the other hand, Leathes has shown that, during absorption, the non-protein nitrogen (that is, the amino-acid nitrogen) of the blood increases. It is assumed, therefore, that amino-acids absorbed by the columnar cells are transferred to the portal vein radicals, and in the portal blood are conveyed to the liver. Here the liver cells appear to "work over" these amino-acids. The right kind and right quantity of amino-acids, to suit the requirements of the tissues, are allowed to pass on in the blood of the hepatic vein; whereas the amino-acids, which are useless to the tissues, and the excess of useful amino-acids, are by the liver cells converted into urea, which is carried round to the kidneys to be excreted.

In order that the tissue proteins of the body may be recouped for the amount of wear and tear which takes place during nitrogenous katabolism, they must be supplied with nitrogen, and this is present in the amino-acids; but in order that the right kinds of amino-acids may be obtained, much food protein has to be digested, and both appropriate and inappropriate amino-acids absorbed by the villi. The nitrogen of the amino-acids is supplied to the tissue proteins to replace that lost in "wear and tear"; the non-nitrogenous portion, like carbohydrate and fat, is available for oxidation, and so for the production of heat. In exceptional circumstances some protein seems to be absorbed as such; for instance, if many eggs are eaten, egg-albumin appears in the urine. This must have been in the blood as such, whence it arrived from the intestine.

ABSORPTION OF FAT.

Moore and Rockwood have shown that fat is not absorbed as fat, but as glycerin and fatty acid or soap. It is generally accepted that the fatty acid set free in the intestine is dissolved by the bile salts, and in this way, together with the glycerin, is absorbed by the columnar cells, but that during absorption a lipase which is contained in the columnar cells re-synthesises, by reverse action, the glycerin and fatty acid. In this way minute fat particles are found near the bases of the columnar cells, and these may be demonstrated by staining with a 1 per cent. solution of osmic acid. The fat globules are further taken up from the columnar cells by some of the lymphocytes, which are capable of exhibiting amœboid movements, and which are found in the lymphoid tissue between the columnar cells and the central lacteal. The fat is then deposited in the central lacteal by these amœboid cells, and in this way it gets into the general lacteal stream, and thence into the thoracic duct. The bile salts, which have been absorbed by the columnar cells, in all probability get into the portal vein radical, and in this way are taken back to the liver to be excreted again in the bile. After a fatty meal minute globules of fat may be demonstrated in the blood plasma of an animal; but they disappear rapidly, possibly existing in a soluble and invisible form adsorbed to the blood proteins before they are deposited in the fat depôts of the body.

ABSORPTION OF CARBOHYDRATE.

During digestion the greater part of the carbohydrate of the food is converted into the glucoses. These are comparatively small molecules which are readily dissolved, and easily passed through the columnar cells into the portal vein radical which lies beneath. It is possible that some maltose may be absorbed by the columnar cells, and that during its passage through those cells it is converted into dextrose before it enters the portal vein radicals. It is possible that in these columnar epithelial cells the glucose, which is being absorbed, is linked to the cell protein, and that, farther down the cells, this loosely combined substance is split into two, the dextrose passing into the portal vein radical and the protein molecule remaining intact in the columnar cells and ready to combine with fresh glucoses to be passed through the cells. A small proportion of the dextrose, which is carried to the liver, goes on unchanged to the tissues to be assimilated, but the greater portion of the absorbed glucose on arriving at the liver is stored there by the liver cells as glycogen.

In summing up the process of absorption, it may be concluded that the absorption of digested food takes place mainly in the small intestine by the aid of the villi. Absorption depends upon the physical processes of diffusion and osmosis, together with the biotic activity of the columnar cells over the villi. And these two processes cannot be separated from one another. The absorbed cleavage products of protein digestion and the absorbed carbohydrates are taken up in the portal vein radicals. The absorbed fat is conveyed to the central lacteal, and the water, with dissolved salts, passes both into the portal vein radical and the central lacteal radical contained in the villi.

ABSORPTION IN THE LARGE INTESTINE.

There are no villi in the large intestine, but a certain amount of absorption does take place here through the columnar cells lining the mucous membrane. The contents of the lowest part of the small intestine are extremely fluid, whereas, in normal circumstances, the contents of the rectum are solid. The conclusion to be drawn, therefore, is that much water and certain substances held in solution are absorbed by the mucous membrane of the large intestine. In special circumstances it is possible that soluble protein, carbohydrate (sugar), and fats may be (very slightly) absorbed from the mucous membrane of the large intestine, because the nutrition of patients is fairly well maintained by administering nutrient enemata or fluids containing substances in solution which are thrown up into the large bowel. The soluble protein absorbed in this way is probably taken by the blood to the tissues. It is probable, however, that cleavage of the large protein molecule takes place before assimilation by the tissues occur. Here the tissue erepsin steps in, and brings about the necessary cleavage. It is found that, in some tissues, the power of the tissue erepsin is even greater than that of the intestinal erepsin.

THE COMPOSITION OF THE FÆCES.

The large intestine excretes—

(1) The residue of the digestive juices; (2) the unabsorbed food; (3) mineral salts, such as iron and calcium salts.

About 6 to 8 oz. of fæces are excreted in the twenty-four hours. The reaction is alkaline; this is due to putrefaction, and is most pronounced on a diet rich in protein.

Composition—

Water, about 70 to 80 per cent.
Solids, 20 to 30 per cent.

The solid portion is made up as follows:—

1. Undigested food, such as yellow elastic tissue, keratin, cellulose, starch, hæmatin, and the excess of digested material not absorbed.

2. Substances excreted, such as mucin, bile, including stercobilin derived from bilirubin, cholalic acid, cholesterin.

3. Salts, such as calcium phosphate and ammonio-magnesium phosphate; the former constitutes the "intestinal sand" which is sometimes excreted in certain diseases.

4. Products of decomposition, such as indole, skatole phenol, also lactic acid and fatty acids.

5. Micro-organisms.

Meconium is the first material passed per anum by the newly born child, and it chiefly consists of bile, mucus, and epithelial débris from the intestinal wall. The colour is due to bilirubin and biliverdin, and not to stercobilin.

CHAPTER XV.

THE MECHANICAL PROCESSES OF DIGESTION AND EXCRETION.

These processes include mastication, brought about chiefly by the movements of the lower jaw, tongue, and cheeks, aided by the teeth; deglutition; the complex movements of the stomach; intestinal movements, and defæcation. As the teeth are so very important in helping in the complete mastication of the food, they will be considered first.

STRUCTURE OF A TOOTH.

The crown of a tooth is that portion which projects beyond the gum. The neck is below the crown; it is somewhat constricted, and surrounded by the free margin of the gum. The root or fang is that portion which is embedded in the jaw after the tooth has completely erupted.

In the middle of a tooth is the pulp cavity, which contains the tooth pulp; this consists of connective-tissue cells, blood vessels, and sensory nerves, but no lymphatics. The pulp is covered with columnar cells (odontoblasts), which line the inner aspect of the dentine or ivory. The dentine, which surrounds the pulp cavity, consists of tubules, projecting along which are fine processes from the odontoblasts. The outer portion of the dentine, beneath the cement, and to a less degree beneath the enamel, forms the interglobular or granular layer; here are the interglobular spaces, into which the dentine tubules open. Dentine chiefly consists of calcium phosphate with a little calcium carbonate, calcium fluoride, and magnesium phosphate. There is a small amount of animal matter which, when boiled, yields gelatin. The enamel, which is the hardest substance in the body, covers that portion of dentine which projects beyond the gum. It consists of elongated six-sided prisms, one end of which is supported on the dentine, the other end being free. Enamel consists of salts similar to those composing the dentine, and contains no animal matter. Surrounding the dentine, which is placed beneath the level of the gum, is the cement or crusta petrosa; this substance helps to fix the tooth in its socket. In structure it resembles bone. It contains lacunæ, in which are branched bone cells and canaliculi, which occasionally communicate with the dentine tubules and the interglobular spaces. The laminæ of the crusta petrosa are fixed together by the perforating fibres of Sharpey, which correspond with the white fibres of connective tissue.

The crusta petrosa is formed from the inner layer of the sac which surrounded the tooth during its development in the jaw. The structure and function of the tooth sac are much the same as the osteo-genetic layer of the periosteum. The outer part of the membrane of the tooth sac forms the dental periosteum, the function of which is to help to attach the tooth to its socket, and also, in connection with the vascular pulp, to nourish the tooth. The dental periosteum also gives rise to cells called osteoclasts, which cause rarefaction of the crusta petrosa and the root of the tooth, and bring about the shedding of the milk teeth.

DENTAL FORMULÆ.

MILK OR TEMPORARY TEETH.

Incisors, $\frac{2-2}{2-2}$; Canines, $\frac{1-1}{1-1}$; Premolars or Bicuspids, $\frac{0-0}{0-0}$; Molars, $\frac{2-2}{2-2}=20$.

PERMANENT TEETH.

Incisors, $\frac{2-2}{2-2}$; Canines, $\frac{1-1}{1-1}$; Premolars, $\frac{2-2}{2-2}$; Molars, $\frac{3-3}{3-3}=32$.

Dentition.—At birth the jaws contain the dental sacs in which the temporary teeth are. The crowns of these are calcified. There is also present the calcified crown of the first molar of the permanent set, which is situated immediately behind the last temporary molar. After birth the sacs enlarge, the edges of the teeth become sharper, and the fangs develop. The edge of the tooth appears beneath the vascular gum, which finally becomes perforated, and the tooth, surrounded by a thin cuticle or membrane called Nasmyth's membrane, is erupted. The temporary set appear for the most part in groups in the following order (Ashby and Wright):—

First group.—The lower two central incisors appear from the sixth to eighth month.

Second group.—The four upper incisors are erupted from the eighth to tenth month.

Third group.—The lower lateral incisors, the upper and lower front molars, appear from the twelfth to fourteenth month.

Fourth group.—The canines appear, the upper ones usually first, from the eighteenth to twentieth month.

Fifth group.—The posterior molars mostly appear at the age of two to two and a half years. The permanent teeth are erupted in the following order:—

First molar	6	years of age.
Central incisors . . .	7	,,
Lateral incisors. . . .	8	,,
Anterior bicuspid . . .	9	,,
Posterior bicuspid . . .	10	,,
Canines	11–12	,,
Second molars . . .	12–13	,,
Third molars (wisdom teeth)	17–25	,,

At six years of age the jaws contain the milk teeth and the unerupted permanent teeth, except the wisdoms or third molars.

Rickets is the commonest cause of delayed dentition, and the teeth are not only erupted later than usual, but the defective nutrition, which occurs with rickets, interferes with the development of the teeth, the consequence of which is that the enamel is defective and easily wears away, the dentine is exposed and readily becomes carious. Defective teeth give rise to dyspepsia through the food being improperly masticated, and carious teeth give rise to poisons, which are readily absorbed from the alimentary canal and cause such diseases as tonsillitis, anæmia, etc.

THE NEURO-MUSCULAR MECHANISM OF THE ALIMENTARY CANAL.

Mastication.—Mastication is a complex voluntary act, the purpose of which is to reduce the food to a condition of minute subdivision, in order that it may present a large area to the activity of the digestive juices, and further to ensure the thorough admixture of the food with the saliva (insalivation). One bone only is involved in the act, namely, the lower jaw, which performs the movements of elevation, depression, protrusion, retraction, and side to side, moving upon the fixed points furnished by the temporo-maxillary articulations. The muscles affecting these movements and their innervation are as follows:—The jaw is raised by the temporals, the masseters, and the internal pterygoids acting simultaneously on both sides; their motor twigs are derived from the motor root (inferior maxillary) of the trigeminal nerve. Depression is mainly a passive process due to the weight of the lower jaw, aided, however, by the contractions of the digastrics, and to a less extent by those of the mylohyoids and geniohyoids. The geniohyoid is supplied by a branch of the first cervical nerve distributed by way of the hypoglossal, while the two former receive twigs from the mylohyoid branch of the inferior dental nerve. Protrusion is effected by the simultaneous contraction of the external pterygoids, whose innervation is derived from the inferior maxillary branch of the trigeminal. Should they act separately, lateral movements are produced. Retraction is the result of the contraction of the posterior fibres of the temporal muscles. These are supplied also by the inferior maxillary division of the fifth nerve. The movements in mastication may be divided into two groups: those of tearing, which chiefly involve elevation, protrusion, and retraction, and the grinding movements between the molar teeth, which still further subdivide the particles torn from the food by the incisor teeth into still more minute particles. These latter movements are produced by a combination of elevation, protrusion, retraction, and side to side movements, effected chiefly by simultaneous and successive contractions of the two external pterygoid muscles. But these movements, though complete, are not sufficient for useful mastication. The food must be returned again and again to the molar teeth, and this is effected by the movements of the cheek (buccinators) and lip muscles supplied by the facial nerve, and by tongue movements produced through the intermediation of the hypoglossal nerve. Mastication is a voluntary process, involving the contraction of many muscles in a perfectly co-ordinate fashion. A "centre for mastication" has been postulated with its seat in the medulla, and afferent impulses play a large part in its guidance. The fifth nerve is the chief afferent nerve involved, as is shown by the fact that bilateral sensory paralysis of the tongue, which in its major part is supplied by the lingual nerve, renders mastication almost an impossibility.

✓ **Deglutition.** — *Movements.* — Majendie, as the result of his classical investigations, divided the act of deglutition or swallowing into three stages. During the first stage the food is passed from the mouth, past the anterior pillars of the fauces, into the pharynx; during the second, through the pharynx, and past the posterior nasal and laryngeal orifices to the superior orifice of the œsophagus; while during the third through the œsophagus; and a fourth stage may be added, the passage of the food through the cardiac orifice of the stomach. It must not be thought, however, that these stages are separated from one another by any time limit; they succeed one another instantaneously.

During the *first stage* of the act a convenient quantity of fully masticated food is collected into a bolus, which is then so manipulated as to lie upon the middle of the dorsum of the tongue; the apex of the tongue meanwhile is brought into contact with the roof of the mouth. Thus far at least the movements are voluntary; the voluntary character of the further movements is open to doubt. A pause is now apparent in the act. Succeeding this there occurs a contraction of the diaphragm, an inspiratory movement commonly designated the "swallowing respiration." Almost simultaneously the tongue muscles come into action, and that organ is pressed up against the roof of the mouth, a movement progressing from the apex to the base of that organ. The bolus is thus forced back, past the anterior pillars of the fauces—ridges produced in the mucous membrane at the side of the buccal cavity by the underlying palato-glossi muscles—into the pharynx. One condition is apparently necessary for the progress of the first stage of deglutition, namely, moisture. It is almost impossible to swallow if the mouth and food are dry.

The *second stage*, and the most complicated, comprises the passage of the food through the pharynx, and past the apertures of the nose and larynx. The time of this passage, however, must obviously be short. The pharynx is a chamber common to the passage of alimentary and respiratory products, and should deglutition be a lengthy process there is danger of suffocation. It was formerly believed that the bolus was propelled through the pharynx by the peristaltic contractions of the pharyngeal constrictors upon it; but it has been demonstrated by Kronecker and Meltzer that it is not the contraction of these muscles, but rather the short, sharp, and sudden contraction of the mylohyoid muscles, which furnishes the necessary acceleration to the bolus. These muscles contract at the beginning of this stage, and their effort is aided by the almost simultaneous contraction of the stylo-glossi, hyo-glossi, and palato-glossi muscles. The two former pull the tongue backwards and downwards, thus increasing the pressure in the mouth, and their efforts to shut off the mouth cavity from that of the pharynx are still further aided by the contractions of the latter. In its descent the bolus is guided by the contraction of the soft palate, uvula, and palato-pharyngei, and is further prevented, by their contraction, from making a false passage into the nasal cavities. If the muscles of the soft palate are paralysed, during this stage of swallowing, the posterior nares are not shut off from the cavity of the pharynx, and consequently fluids are liable to regurgitate into the nose. The soft palate is elevated by the contractions of the levatores palati, the uvula is elevated by the action of the azygos uvulæ muscles, and comes into contact with an elevation on the posterior wall of the pharynx. At the same time the palato-pharyngei are rendered tense, and move inward. The palato-pharyngei, or rather the overlying mucous membrane constituting the posterior pillars of the fauces, form, as it were, a pair of curtains with the uvula lying between them. As a result of this series of muscular activity the nasal cavities are completely cut off from the pharynx, and a sloping surface is formed, directed from above downward and from before backward, from the palate to the posterior wall of the pharynx, which serves to direct the course of the bolus hurled against it as the result of the mylohyoid contraction. The bolus has then to pass the larynx, and, in order that this may be accomplished safely, many muscles of the latter structure are called into activity. The changes may be summarised thus,—first and most important, the larynx is elevated. This can be easily seen on superficial examination. Moreover, it is an essential process of the act of deglutition, for if the larynx is held the act becomes impossible. This elevation is the result of the activity of the thyrohyoids, digastrics, geniohyoids, and the mylohyoids. Accompanying this are other muscular activities. The arytenoid cartilages are drawn forward from the posterior wall of the pharynx, against which they usually lie, by the contraction of the thyro-arytenoids. At the same time, they are approximated by the action of the arytenoideus, and their processes vocales are rotated inward by contraction of the lateral crico-arytenoid, thus producing adduction of the true vocal cords and widening of the pharyngeal orifices. At the same time, this adduction is not of supreme importance for the act, for it has been shown that an animal will still swallow normally even if an instrument is thrust between the vocal cords. Of much greater importance is the elevation of the larynx previously mentioned. Simultaneously the constrictors, the aryteno-epiglottidei, at the superior aperture of the larynx are called into play. With regard to the actual movements of the epiglottis, discussion has arisen. It was formerly thought that it was closed down like a lid over the laryngeal orifice, but this does not seem to be the case. According to the researches of Anderson Stuart, it appears that it is simply the crowding together of the parts at the base of the tongue which protects the superior laryngeal orifice. The epiglottis is not folded over, its anterior aspect remains in contact with the base of the tongue, and food passes over, not its anterior but its posterior aspect. While the food passes over the top of the larynx, respiration is reflexly inhibited. If, however, inspiration suddenly occurs, food may enter the larynx and produce reflex coughing.

During the *third stage* the food is passed down through the œsophagus to the cardiac orifice of the stomach. If the bolus is of small size, or of liquid nature, it is passed down through the œsophagus simply as a result of the energy imparted to it by the mylohyoid contraction. It may even pass through the cardiac orifice into the stomach. The passage of the bolus, or liquid, is succeeded by the peristaltic contraction of the œsophagus. That this is actually the case is proved by post-mortem examination where corrosive solutions, such as sulphuric acid and corrosive sublimate, have been swallowed; corrosion is only apparent at the three positions where the œsophagus is narrow,[1] not along its whole length, as it would be were the liquid dependent for every step of its forward progress upon the peristaltic contractions of the œsophagus upon it. In this case the total time of passage amounts only to one second. With a larger bolus conduction is slower, for in this case it is carried downward by the peristaltic contraction of the œsophagus. In front of a bolus the œsophagus is inhibited and dilated; behind it the circular fibres are contracted, and it is consequently forced downward. The time taken by the complete process of passage of the bolus through the œsophagus is six seconds. In the upper part of the œsophagus the conduction is quicker than in the lower. This is due to the fact that in the upper third the muscular coat of the œsophagus consists entirely of the more quickly contracting striated muscle, whilst the lower third consists of plain or more slowly contracting muscle. The middle third occupies an intermediate position with regard both to time relations and to the histological character of its muscle coats. Kronecker and Maltzer thought each of these thirds contracted separately, but Cannon and Oloser showed, by feeding an animal with food containing bismuth subnitrate and using the X-rays, that this is not the case. The peristaltic contraction of one third passes without any interval over the next third.

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[1] The œsophagus presents three constrictions, the uppermost being at its commencement behind the cricoid cartilage, the middle one where it is crossed by the left bronchus, and the lowermost one at the cardiac orifice of the stomach.

Having reached the cardiac orifice of the stomach, the *fourth stage* of deglutition occurs. If the bolus is small, or the food liquid, it may be shot directly from the mouth into the stomach, even although the circular fibres of the œsophagus may form a ring at the orifice. This ring is due to the cardiac sphincter muscle, which is normally in a state of contraction. On the other hand, the food may stay above the cardiac orifice until the peristaltic wave reaches the orifice, when the contraction of the muscle at the cardiac orifice is inhibited and the food is shot into the stomach. In the case of a larger bolus the food does not pass into the stomach until it is forced through the orifice by peristaltic waves.

Should a second swallow be made during the progress of the first, *i.e.* before the lapse of six seconds after the first, the œsophageal movements are inhibited, and the food is allowed to fall through the œsophagus to the cardiac orifice. When movements of deglutition have ceased a peristaltic contraction of the œsophagus occurs, and sweeps the masses of food into the stomach. In ruminants, after food has been swallowed, it may be returned to the mouth for further mastication ("chewing the cud" or rumination); this return is due to reverse peristalsis in the œsophagus, which occasionally occurs in human beings.

Nervous Mechanism of Deglutition.—Swallowing is on the whole a complicated involuntary reflex act. At the same time, however, it can be initiated voluntarily, so that it must be regarded to a certain extent as under the control of the will. But even in this case it is not the whole process which is effected by the will, it is merely that the initial stimulus necessary for the reflex complex—namely, stimulation of the anterior pillars of the fauces—is supplied by stimulation of the fauces by the tongue. The sensory area, from which the reflex is elicited, lies in the immediate vicinity of the anterior pillars of the fauces and of the tonsils. The *afferent* nerves concerned are the superior maxillary division of the fifth nerve, pharyngeal branches of the vagus, glosso-pharyngeal, and the superior laryngeal. Stimulation of the superior laryngeal branch of the vagus produces reflex movements of deglutition. The *efferent* impulses travel down the following nerves: by the mylohyoid branch of the trigeminal to the mylohyoid muscle; by the branches of the glosso-pharyngeal, vagus, and spinal accessory, as well as by the fifth cranial nerves to the pharyngeal, palatine, and laryngeal muscles involved; by the hypoglossal to the tongue, and by the phrenic to the diaphragm. Even the peristaltic contraction of the œsophagus is reflex; thus, if the œsophagus is severed, with the nerves uninjured, contraction of the pharyngeal and œsophageal ends will still occur at appropriate intervals after initiation of deglutition movements. Moreover, stimulation of the œsophageal mucous membrane produces no response. In this case, therefore, we have to carefully distinguish between a peristaltic movement, produced by the central nervous system, and such a peristaltic movement as that obtained from the intestine, which depends upon the integrity of certain peripheral nervous structures, *e.g.* the plexuses of Meissner and Auerbach.

The muscular tissue of the œsophagus is arranged in two layers, an external longitudinal and an internal circular. Contraction of the outer layer produces dilatation of the tube, contraction of the inner, constriction. Consequently, in a peristaltic movement of the œsophagus both sets come into activity, and at any point contraction of the longitudinal fibres precedes that of the circular. In addition there is a muscularis mucosæ, consisting of longitudinal fibres situated in the deepest layer of the mucous membrane.

As regards peripheral nervous structures in the œsophagus, there are two ganglionated plexuses of nerve fibres, situated one in the muscular and the other in the submucous coat. The motor nerves to the œsophagus are the vagi. Stimulation of the peripheral end of the cut vagus nerve produces peristaltic movements of the œsophagus. In addition, however, it produces inhibition of the cardiac sphincter. Its section causes this opening to be thrown into a condition of tonic spasm. Consequently, the vagus must be regarded as the inhibitory nerve of the cardiac sphincter. The œsophagus is a visceral structure, and therefore must be innervated through a sympathetic ganglion,—that is to say, at some place in the course of the nerve fibres going to the œsophagus there must be a local cell station. This cell station is peripheral, in connection with the ganglia present in the organ itself,—at least, this is found to be so in the cat.

Since the movements of deglutition are of such wide extent, and are yet executed so orderly, it has been assumed that a centre for deglutition must exist in the medulla (Marckwald), and because of the fact that respiratory inhibition always accompanies deglutition, it has been assumed that the centre stands in close relation to the respiratory centre. The respiratory inhibition during deglutition is also the result of a reflex, the afferent nerve involved being the glosso-pharyngeal. Stimulation of the central cut end of this nerve produces respiratory inhibition for a period of from five to six seconds, *i.e.* time for a complete act of deglutition.

MOVEMENTS OF THE STOMACH.

Neuro-muscular Mechanism. — The musculature of the stomach consists of unstriated, involuntary muscle fibres. These are arranged in three layers. The outermost coat is composed of fibres having a longitudinal direction continuous at the cardiac orifice with the longitudinal layer of the œsophagus; these fibres are especially well marked at the curvatures, being thin and ill defined over the anterior and posterior surfaces of the organ. At the pylorus this coat is again collected into the longitudinal coats of the intestine. The internal or oblique coat is somewhat ill defined, and seems to be continuous with the circular coat of the œsophagus, and is spread out over the fundus and body of the stomach. At the pyloric end it apparently becomes continuous with the middle or circular coat of the intestine. The middle or circular coat over the fundus and body is not well defined, but traced towards the pylorus it rapidly increases, becoming the thickest of all the coats. It is especially thickened at two places, forming rings of muscle tissue or sphincters. One of these is at the pylorus constituting the pyloric sphincter, separating the stomach from the duodenum ; the other, the sphincter of the pyloric vestibule or the "transverse band," is situated to the left of the pyloric sphincter, and the region between it and this sphincter is known as the vestibule of the pylorus.

In the deepest part of the mucous membrane there is the muscularis mucosæ, consisting of two layers—longitudinal and circular.

The nerves of the stomach, which are derived from the vagi and the sympathetic, are distributed in two sheaths. One of these sheaths, which lies between the longitudinal and the other coats of the stomach, is Auerbach's plexus. This consists of a plexus of non-medullated nerves, at the nodes of which are nerve cells. Lying in the submucous coat is the plexus of Meissner, similar to that of Auerbach, except that its fibres are finer and that it contains fewer nerve cells. These plexuses are continued down the alimentary canal from stomach to anus.

Movements of the Stomach.—When devoid of food the stomach remains in a condition of slight tonic contraction, the mucous membrane being thrown into folds. X-ray observations have shown that in the empty condition only the pear-shaped upper third of the stomach contains gas, the rest of the organ passing to the pylorus in the form of a collapsed tube, which corresponds in position to the small curvature of the filled stomach (A. F. Hertz). Food when swallowed causes relaxation of the walls of the stomach. Moreover, the food introduced at different times bears different relations with regard to the stomach walls. That is to say, food first introduced is spread round the stomach, forming a lining to the mucous membrane. Food introduced later is retained encapsuled like a ball by its enveloping layer of mucin. This fact is of extreme importance, for the later food is protected from the gastric juice, and the admixed saliva, which is inactive in an acid medium, is enabled to prolong its activity. Cannon maintains that salivary digestion may proceed even for an hour or more after the food is in the stomach. Soon after the introduction of food into the stomach, movements begin. These proceed at first very gently, but later on increase in intensity. They are confined entirely to the pyloric portion of the stomach. Cannon, by his recent feeding experiments with bismuth subnitrate and X-ray observations, has succeeded in observing the movements of the stomach very closely. They consist of a series of contractions, which proceed in a peristaltic manner. The sphincter at the commencement of the pyloric vestibule contracts in a ring-like manner, and this contraction is propagated over the pyloric portion. The time taken in transit is twenty-six seconds (in the cat), and the successive contractions follow one another at ten seconds intervals. By this means the food in the pyloric region of the stomach is thoroughly disintegrated and mixed with the gastric juice. When this condition is reached the pylorus is relaxed at certain intervals, and portions of the acid chyme are ejected into the duodenum. Immediately succeeding this, the pylorus again enters into tonic activity. The relaxations of the pylorus coincide with the arrival, at that place, of a wave of contraction, although they are irregular; for every peristaltic wave there is a corresponding pyloric inhibition. The mechanism of pyloric regulation will be discussed later. It is in the pyloric vestibule of the stomach that the food is so thoroughly mixed with the gastric juice, and it is here also that solid food is most likely to injure the mucous membrane of the stomach, and so predispose to the formation of gastric ulcer (*vide* p. 107). So far no mention has been made of the functions and movements of the fundus and body of the stomach. These portions do not undergo contractions in rhythmic series, but the musculature enters into a condition of maintained strong tonicity. The function of this is obvious, and is to replenish the pyloric triturating apparatus with further materials from the fundus and body store.

Movements of the Pylorus and their Regulation.—It has been already mentioned that the food is retained in the stomach, and the pylorus not relaxed until the food has been reduced to an appropriate stage of thinness, and until the gastric juice had been thoroughly admixed with the food. These two conditions are the necessary factors in the opening of the pyloric sphincter. So long as the food on the cardiac side of the sphincter is solid the sphincter will not relax. Further, if it is in a relaxed condition, and pieces of solid food come in contact with it, contraction occurs at once. This contraction of the pylorus, due to large portions of food in the stomach, may cause "stomach ache." On the other hand, this mechanical condition is not sufficient alone to cause pyloric opening. The other factors necessary are acidity and warmth. It is only when the gastric contents have reached a certain degree of acidity, and are in the necessary physical condition of subdivision, that the sphincter is relaxed. Warmth is supplied by the normal gastric contents, but in cases of painful spasm of the pylorus, relaxation may be brought about by the internal administration of hot liquids and the external application of hot light poultices. The relaxation of the pylorus, however, is not continuous but intermittent. This is due to the fact that acid on the duodenal side of the sphincter causes its contraction. Consequently, the course of the change may be pictured thus: the acid on the gastric side of the sphincter inhibits its action, and by peristaltic contractions, the acid chyme is ejected into the duodenum. Arrived here it causes pyloric tonic contraction, and until the acid is neutralised by the alkaline juices in the duodenum pyloric relaxation is an impossibility. Different foods also appear to exert different influences upon the sphincter. Proteins are retained in the stomach twice as long as carbohydrates, and fats are kept for a longer period still (Cannon).

Recently, Boldireff has stated that regurgitation from the intestine into the stomach is a normal process, and has brought forward strong evidence in favour of his views. It is in this way that more fat is split in the stomach than can be accounted for by the small amount of gastric lipase present.

Production and Regulation of the Movements of the Stomach and Pylorus.—The stomach is connected with the central nervous system by the vagi and the sympathetics. The vagus fibres have their cell station, just as in the case of the œsophagus, in the peripheral ganglia in the wall of the organ (Auerbach's plexus); whilst the sympathetic fibres which leave the cord in the fifth, sixth, seventh, and eighth anterior roots of the thoracic nerves pass to the stomach, via the splanchnics, the connection between pre-ganglionic and post-ganglionic neurones being made at the cœliac ganglia. Stimulation of the vagus produces contraction of the stomach, *i.e.* it is the motor nerve of the stomach. On the other hand, the sympathetic fibres are inhibitory, their stimulation producing gastric relaxation. If, however, the stomach of an animal is full, and that stomach is removed completely from the body, all nervous connections being necessarily severed, and it is placed in oxygenated and warm Ringer solution, its contractions will still proceed in a normal manner (Hofmeister and Schutz). Aldehoff and von Mering found that the tone and peristalsis of the stomach and the pyloric reflexes remained normal for months, after both vagi had been cut just below the diaphragm, and also after destruction of the cœliac plexus or division of the splanchnic nerves. These results were confirmed by Cannon by X-ray observations on the stomachs of cats after section of the vagi and the splanchnic nerves (A. F. Hertz). Consequently the impulses, which are transmitted through the vagi and sympathetic nerves, are simply controlling impulses; the power of contraction is resident in the stomach itself, but whether it is due to the activity of the intrinsic ganglion cells or to the muscular tissue itself is an open question. The balance of evidence is in favour of the *latter* hypothesis. The influence of the nervous system upon the movements of the stomach is well shown by the influence of psychical conditions. Anger or pain at once stop gastric movements; these impulses probably descend in the vagi. It is possible, therefore, that the vagus can exert both a stimulating and an inhibitory influence upon the movements of the stomach. Similarly, the movements of the pylorus, although regulated, are not normally produced by the activity of the central nervous system. After section of the vagus and sympathetic, these movements proceed exactly as before. It is interesting to note that the sorting out action of the stomach, previously mentioned, *i.e.* carbohydrates passing through the pylorus more quickly than fat or protein, still remains in these circumstances. The closure of the pylorus is due to reflex movement, the path of which is provided by Auerbach's plexus (Cannon). The vagus nerve is the motor nerve of the pylorus: the sympathetic, the inhibitor.

Vomiting.—In vomiting the gastric contents do, and even the contents of part of the small intestine may, take an abnormal direction, and find an exit by the œsophagus, pharynx, and mouth.

The sequence of events is as follows:—There is a feeling of nausea, often accompanied by a large secretion of saliva, and there may be profuse perspiration, and a cold, clammy feeling about the hands and face. The movements known as retching quickly follow. These are really abortive inspiratory movements, since they are made with a closed glottis. After one or two of these ineffectual efforts at inspiration the expiratory muscles enter into a condition of modified activity: modified to the extent that the abdominal muscles are contracted, as is also the diaphragm; consequently the pressure in the abdomen, and therefore the pressure on the stomach, are increased. Moreover, the glottis being closed and the diaphragm descending, the negative pressure in the thorax is increased.

Simultaneously with these changes the stomach has not been inactive. During the early part of the act the cardiac orifice becomes greatly dilated. Subsequently a series of about twelve contraction waves make their appearance, travelling from a little below the cardiac orifice to the pylorus. They are succeeded by a firm contraction of the sphincter of the pyloric vestibule and of the pyloric canal of the stomach. Coinciding with the contraction of the abdominal muscles, the fundus is relaxed and flaccid, the pylorus firmly contracted, and the cardiac orifice dilated. The effect of the sudden abdominal contraction is to drive the gastric contents up into the œsophagus, which shortens; this is due to the contraction of its longitudinal muscular coat. Simultaneously, the glottis being protected by its constrained closure from the very first stage of the act, the naso-pharynx is as a rule cut off by the increased tension of the soft palate (levator palati and tensor palati muscles), the elevation of the uvula (azygos uvulæ), and the approximation of the posterior pillars of the fauces (palato-pharyngei). Occasionally, however, the barrier thus opposed is broken down, and the vomit may pass through the nose.

The convulsive movement of the anterior abdominal muscles would appear, *a priori*, to show that their contraction furnishes the major part of the energy necessary for the process of vomiting. Still, it has been a much contested point as to whether the stomach or the abdominal muscles play the more important part in the process. The evidence at hand is that provided by Majendie's and Gianuzzi's experiments. Majendie substituted a bladder for the stomach, and still produced vomiting by injecting tartar emetic. Gianuzzi demonstrated that vomiting could not be produced in a curarised animal. Consequently it appears that the abdominal muscles are the most important agents in the process. Vomiting, however, is possible even when the abdominal muscles are paralysed, which shows that the stomach wall itself contracts. The pylorus, too, does not always remain tightly closed; for in cases of strangulation of the gut (strangulated hernia), bile and the contents of the small intestine may reach the stomach and be vomited.

The Vomiting Centre.—Since vomiting involves such a very large field of musculature, both of the voluntary and involuntary variety, and since its various movements are so peculiarly adapted to the fulfilment of the purpose of a particular aim, namely, the removing of offensive material from the stomach, it is believed that in the medulla there is a co-ordinating "vomiting centre." This centre is placed in close relationship to the respiratory and vasomotor centres. The close relationship of the vomiting to the respiratory centre may be understood from the following facts. Irritation of the respiratory centre, occasioning dyspnœa, frequently induces vomiting; the production of apnœa, by taking a series of long deep breaths, may stop vomiting after a feeling of nausea has occurred:

This centre may be regulated and controlled in a number of different ways.

1. It may be excited directly by apomorphine, the action of which is best explained as being due to stimulation of the vomiting centre. The centre seems to be excited also by cerebral anæmia, the vomiting, which follows such cerebral anæmia, is in the ordinary course associated with contraction of the diaphragm and the abdominal muscles; this raises the intra-abdominal pressure. The result is the emptying of the abdominal veins into the right side of the heart through the inferior vena cava; the arterial blood pressure is consequently raised and the cerebral anæmia overcome.

2. *Afferent Impulses.*—The vomiting centre may be ex-

cited reflexly in many ways. The most usual reflex is that obtained from the mucous membrane of the stomach through stimulation of the vagus endings. This may be produced by emetics, such as mustard, or by abnormal products of digestion. Another well known reflex is that produced by stimulation of the back of the pharynx with the finger or a feather. The afferent path is through the glosso-pharyngeal nerve. Similarly irritation of various abdominal and pelvic organs will cause reflex vomiting. As examples may be mentioned gall-stones irritating the bile passages, inflammation of the pancreas and peritoneum, calculi in the urinary passages, strangulation of the intestine, a pregnant uterus, injury to the ovary or testicle. In each case the afferent impulse probably travels to the vomiting centre via the vagus. Higher reflexes, such as psychical influences produced by disgusting sights and smells, will cause vomiting.

A reflex vomit is also obtained through the disturbance of the organs of equilibration, such as the cerebellum and the semicircular canals. It is possible that sea-sickness may be due to the latter reflex by way of fibres in the vestibular division of the auditory nerve.

3. *Efferent Impulses.*—These impulses travel from the centre in many ways :—to the salivary glands by the chorda tympani and tympanic branch of the glosso-pharyngeal ; to the stomach walls, the pyloric sphincter, and the cardiac orifice by the vagi ; to the laryngeal and palatine muscles by the vagi, spinal accessory, and glosso-pharyngeal nerves ; to the diaphragm by the phrenics, and to the abdominal muscles by the thoracic nerves.

Emetics, or drugs which produce emesis or vomiting, may be divided into two classes : *Central emetics*, those which act directly upon the vomiting centre, like apomorphine ; and *peripheral emetics*, those which act upon the mucous membrane of the stomach, such as sodium chloride, zinc sulphate, mustard, copper sulphate, and tartar emetic.

The Movements of the Small Intestine.—*Neuro-muscular mechanism.*—The musculature of the small intestine is of the unstriated or involuntary variety. It is arranged in two main layers, which together form the outermost intestinal coat, and which are separated from one another by a small amount of connective tissues. The outermost coat consists of longitudinally directed fibres; in the inner coat the fibres are disposed circularly. The remaining muscle fibres of the intestine are collected together into the muscularis mucosæ. This is a double layer of plain muscle lying at the boundary between the mucous membrane and the submucous tissue. The nervous tissue is arranged in precisely the same manner as in the stomach,—that is to say, in the connective tissue between the outer and inner coats of the intestine, there is situated the relatively coarse plexus of Auerbach. In the submucous tissue the delicate plexus of Meissner is placed.

The movements of the intestines can be studied by opening the abdomen of an animal which has been recently fed and then anæsthetised. In order to protect the intestines from the injurious effects of drying, the operation should be conducted in a bath of warm normal saline solution (0·9 per cent.). Exposed under these conditions, the intestines are observed to be extremely vascular, and to present two kinds of movements—the *peristaltic*, and *movements of rhythmic segmentation.* If the viscera are exposed to the air the movements of the intestines tend to become excessive and disorderly.

Peristaltic Movements.—Under the conditions mentioned above, waves of contraction may be observed progressing slowly down the intestines. Should they not be apparent, they can be easily produced by the introduction of a bolus of any solid material not detrimental to the intestinal mucous membrane. It can be seen, then, that immediately below the introduced body the intestine is inhibited, that is to say, it is relaxed; while, immediately above it, a strong contraction of the intestine is observable. The effect of this is to drive the mass along the intestine. At every stage of its progress the inhibition and contraction of the intestine are evident, and always bear the same spatial relationship to the bolus. Such a movement is termed a peristaltic movement, and may be defined as a quick succession of waves of inhibition and contraction passing slowly along the intestine. The rate of progress is slow. A peristaltic movement takes three and a half hours to progress from the pylorus to the ilio-cæcal valve. In man, after a bismuth meal, the shadow appears in the cæcum about four hours after food is taken, and this leaves the stomach about half an hour after its entry there. Hertz concludes that the average rate at which the contents of the small intestine travel is about one inch per minute. The peristaltic wave does not traverse the small intestine uniformly from one end to the other. The contents of the intestine are moved in an irregularly "pendulum-like" fashion: first onwards, then a little backwards, then onwards once more. Peristaltic waves, then, are, under normal conditions, produced by the stimulation exerted upon the intestinal mucous membrane by the presence of food material. In the case of fasting animals the intestines are empty and tonically contracted, but are quiescent, exhibiting no movements. Other stimuli, however, are efficient; thus a crystal of NaCl applied to the intestinal wall causes a contraction above it and an inhibition below. A pinch produces a precisely similar effect (Starling). Inco-ordination of the peristaltic movements, in which relaxation in front does not coincide with the contraction behind, results in intestinal colic.

The Rhythmic Segmentation Movements.—The movements described above have as their physiological function the driving of the food onwards. The purpose of the rhythmic segmentation movements is the thorough mixing of the food with the intestinal juices. They can best be studied by the X-ray method, the animals being previously fed with material containing bismuth subnitrate (Cannon). The movements are not apparent on alterations of the position of the various loops of intestine ("swaying movements"), but, actually, their most important characteristic is a rhythmical contraction of the circular fibres of the intestine. These constrictions appear at the rate of ten in a minute and a half, and are propagated at the rate of 2 to 5 cms. per second down the intestine (Starling). They may arise at any point. The rate and extent of these constrictions can be directly measured by introducing a balloon into the lumen of the intestine, and connecting it with a Marey's recording tambour. These rhythmic segmentation movements are very vigorous in hunger, and an exaggeration of these movements in nervous subjects is the cause of borborygmi.

The Mechanism of the Peristaltic Movements. — The peristaltic movements may be elicited by a pinch applied to a piece of isolated intestine lying in an oxygenated Ringer's solution. Evidently, then, peristalsis is a movement inherent in the tissues of the intestines themselves, and quite independent for its production upon extraneous influences. As has been pointed out, both muscle and nervous structures are present in these tissues, the question consequently arises as to whether the peristalsis is dependent alone for its production upon muscular conduction (*i.e.* is it myogenic and myodromic?), or whether it is due to the intermediation of Auerbach's plexus (*i.e.* is it neurogenic and neurodromic?). The balance of evidence supports the latter alternative. The peristaltic movements are usually regarded as reflex, due to conduction through Auerbach's plexus—that is, they are *neurogenic.* The evidence in favour of this is—

1. Its complexity, and the fact that the inhibition and contraction so regularly and constantly occur on intestinal stimulation.

2. The peristaltic movements are destroyed, and cannot be revived by any kind of stimulation after the intestine has been treated with cocaine or nicotine. These drugs destroy the activity of nervous structures only, hence it is assumed that peristalsis must be a nervous function (Bayliss and Starling).

3. *The observations of Mall.*—Mall removed a piece of the intestine, and, after reversing it, sutured it to the rest of the intestine. Its former rectal end then lay cranialwards. Under these conditions great disturbances of nutrition occurred, and on post-mortem examination, although the resected piece of intestine was dilated, the food had accumulated at its "head" end. This shows that, normally, the peristaltic waves are conducted in one direction only. Anti-peristaltic waves, however, do occur in abnormal circumstances, *e.g.* in acute intestinal strangulation.

As a result of these considerations, it is concluded that peristalsis is a reflex movement, peculiar, amongst all other reflex movements, because the entire nervous reflex arc (*i.e.* the plexus of Auerbach) is confined to peripheral tissues.

Mechanism of the Rhythmic Segmentation Movements.—These movements occur also in a piece of isolated intestine in warm oxygenated Ringer's solution. But they are not destroyed by the action of nicotine or cocaine upon the intestine. Furthermore, they are produced when the intestine is pinched, and under these conditions, will pass both up and down the intestines. It is concluded, therefore, that these movements are muscular. They are conducted from muscle fibre to muscle fibre without the intervention of any nervous structure, and are therefore of myogenic origin and myodromic in transmission.

Nervous Control of Intestinal Movements.—Although the movements of the intestine are entirely automatic—that is, independent of the central nervous system, yet their regulation and control are functions of this system (*vide* p. 563). To the intestines two sets of efferent nerves pass,—the vagus and the sympathetic. The vagi have their cell stations in the organ itself (*i.e.* in the terminal ganglia). The sympathetic fibres are derived from the anterior roots of the lower six dorsal and upper three lumbar nerves; they leave the anterior roots of these spinal nerves, and pass via the white rami communicantes and the splanchnic nerves to the semilunar ganglia. Here they have their cell station, and their post-ganglionic (non-medullated) fibres are continued on to the intestine. Stimulation of the vagus after a long latent period produces augmentation of the intestinal movements. Sympathetic stimulation, on the other hand, after a short latent period causes inhibition of the movements. Consequently, the vagus is the motor nerve to the intestine, whilst the sympathetic is the inhibitor. At the same time, the vagus is believed to contain some inhibitory fibres. The intraspinal connections of these viscero-motor and viscero-inhibitor fibres are not known, but there is some evidence at least to indicate that there must be connection with the higher parts of the brain. As in the case of the stomach, psychical states are known to exert an influence over the intestinal movements. In the splanchnics, as well as in the viscero-motor (inhibitory) nerves *to* the intestine, there are afferent fibres *from* the intestine. Under normal conditions the subject is not conscious of the intestinal movements; when they become excessive, however, they give rise to painful sensations. Through these afferent nerve fibres, moreover, certain important reflexes are mediated. Thus vomiting may be produced by irritation of the intestinal mucous membrane, and a well-known effect produced is the inhibition of the heart obtained by tapping the intestines (Goltz's tapping experiments).

The sympathetic nerves also contain vasomotor fibres. If the sympathetic nerves to the small intestine are cut there follow local vasodilatation and an increased secretion of watery succus entericus.

Movements of the Large Intestine. — *Neuro-muscular Mechanism.*—The musculature is arranged in the same manner as it is in the small intestine, with only one distinction,—that, in man, the longitudinal fibres are accumulated very largely into three bands which lie on the front and lateral aspects of the cæcum and colon. Similarly, the nervous mechanism consists of the plexuses of Auerbach and Meissner, which, as previously mentioned, are continued along the whole course of the intestine from the upper part of the œsophagus to the lower part of the rectum.

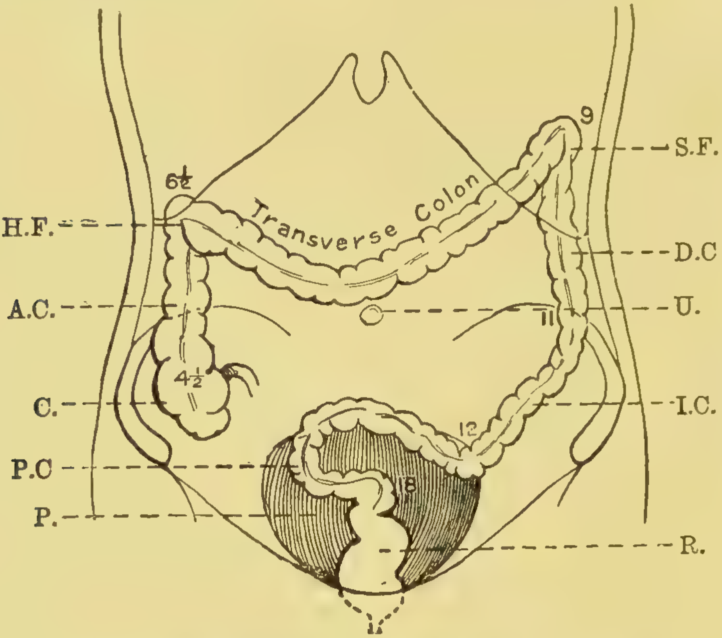

FIG. 14.—Diagram of the large intestine. (A. F. Hertz.)

The pelvic colon *P.C.* is represented in the position it occupies when full. The numbers represent the hours after a bismuth breakfast at which the different parts of the colon are reached. *I.C.*, Iliac colon ; *P.*, Pelvis.

Cannon is mainly responsible for the conceptions of the movements of the large intestine. His experiments were performed upon cats. In these animals the course of the food, in its passage through the alimentary canal, was rendered evident to the X-rays by admixture with bismuth subnitrate. As a result of his experiments he divides the large intestine into two parts :—

1. Extending from the ileo-cæcal valve to the splenic flexure ; and,

2. From the splenic flexure to the pelvic colon. In the

first part of the colon the movements are peristaltic and retro-peristaltic; that is, retro-peristaltic contractions appear at some point in the ascending or transverse colons, and pass back towards the ileo-cæcal valve. Regurgitation into the ileum is prevented by the closure of the ileo-cæcal valve and the ileo-cæcal sphincter (innervated by the splanchnic nerve). The result of this is that there is greater time allowed for the absorption of moisture from the intestinal chyme, for it is very liquid when it reaches the ileo-cæcal valve. In the descending colon a different scheme obtains. In it ordinary peristaltic movements occur, forcing the fæcal mass down into the pelvic colon and rectum. The transition of material from the transverse into the descending colon, in spite of anti-peristaltic movements, is due to the constant pressure exerted behind by the small intestine. Hertz has investigated the rate of the movements of the contents of the colon in man by previously feeding him with a bismuth meal, and examining the shadows caused by the bismuth with X-rays. As a result of these investigations, he finds that, if a "bismuth breakfast" is taken at 8 a.m., the bismuth arrives in the cæcum at 12.30 p.m., at the hepatic flexure at 2.30 p.m., at the middle of the transverse colon at 4 p.m., at the splenic flexure at 5 p.m., and in the pelvic colon at 10 a.m. next day.

Nervous Control of Movements.—There are two distinct nerves, the function of which is to control the automatic intestinal movements. One is viscero-motor, and the other viscero-inhibitor. The viscero-inhibitor impulses run in the splanchnic fibres arising from the cord at a level corresponding with the second, third, and fourth lumbar nerves, and have their cell station in the inferior mesenteric ganglion. The post-ganglionic fibres reach the colon and rectum via the hypogastric nerves and plexus. The viscero-motor fibres are derived from the pelvic splanchnics, white rami come from the second, third, and fourth sacral nerves (anterior roots), and pass directly into the pelvic plexus. Stimulation of these nerves (nervi erigentes) causes contractions of the muscular coats of the descending colon and rectum, vasodilation of the vessels in these organs, and erection of the penis. Their cell stations lie in the small ganglia in close relation to these organs. The hypogastric nerves are the motor nerves for the internal sphincter ani, whilst the pelvic nerves cause contraction of the musculature of the rectum and dilatation of the sphincter internus.

The normal stimulus for the movements of the large intestine is the presence of food material, especially indigestible food like cellulose, in the intestine.

These movements may be influenced by impulses from the upper part of the alimentary canal; for the taking of food or water frequently starts peristaltic movements in the large intestine.

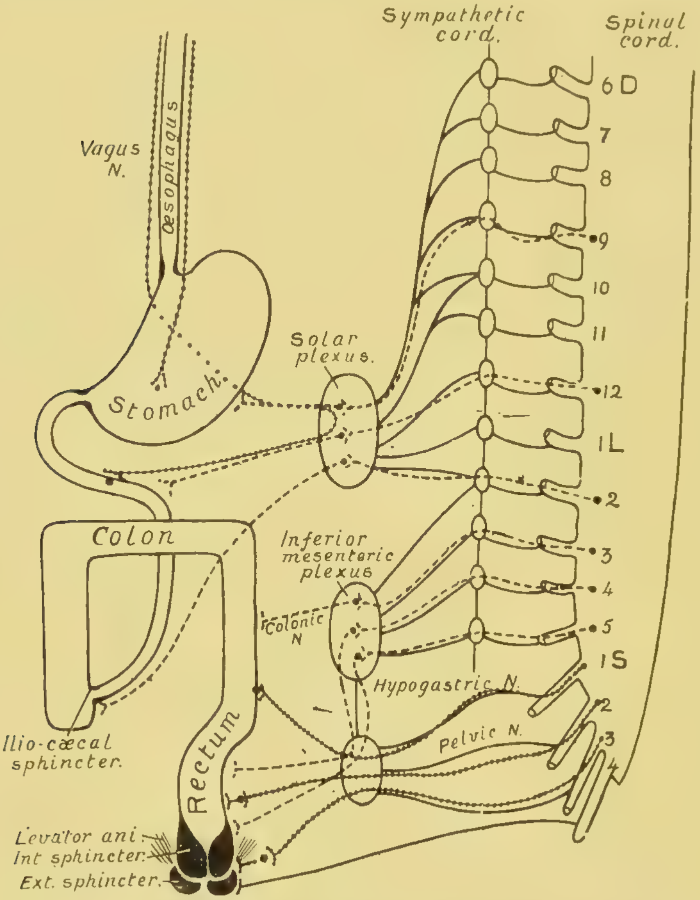

FIG. 15.—Diagram of the nerve supply to the alimentary canal. (A. F. Hertz.)

The movements, however, are influenced by the higher centres; painful sensations inhibit intestinal movements, excitement frequently increases the movements and may cause diarrhœa. Drugs given for the relief of constipation, or of diarrhœa, act on the mucous membrane, thus affecting the secretion; on the muscular wall; or upon the nerve plexuses present. Peristaltic movements are increased by bile; also by the amino-acids, the normal products of the digestion of protein.

Defæcation.—All the indigestible residue of the food, in addition to débris from the alimentary canal and certain intestinal excretions, such as bile and mucin, ultimately reach the lower part of the pelvic colon. Here they are in a state of comparative solidarity, a great part of the moisture present having been absorbed as the result of the retro-peristaltic movements in the ascending and transverse colons previously described above. Ultimately, however, the normal peristaltic movements of the descending colon force some of the fæces into the rectum. The rectum is thrown into a condition of tonic activity, but at the same time its sensory nerves are stimulated, and this is the necessary stimulus for the performance of an act of defæcation, which, however, does not occur immediately on the reception of this stimulus. In normal circumstances, the stool passed to-day is probably derived in chief measure from the food of the day before yesterday (Hutchison).

NEURO-MUSCULAR MECHANISM OF DEFÆCATION.—Defæcation is under the control of the will, and certain voluntary or striated muscles are in a contracted state, holding tight the anal orifice. These muscles are the external sphincter ani, and when the stimulus is very strong, certain perineal muscles, notably the levatores ani, especially in its pubo-rectalis portion.

As a result of this sensory or afferent stimulation, certain voluntary and involuntary movements are made. The chief features of the voluntary side are: the closure of the glottis, fixation of the diaphragm, and a strong contraction of the abdominal muscles, accompanied by inhibition of the sphincter ani externus, and, if in activity, of the levatores ani too. Simultaneously, the involuntary musculature becomes active; the descending and pelvic colon and the rectum are thrown into a series of very strong peristaltic contractions, whilst the sphincter ani internus is relaxed. The voluntary muscles, the levatores ani, moreover, assist in emptying the last traces of fæces from the rectum, namely, by a strong contraction they draw the rectum up over the fæcal mass.

Normally, this complex range of movements, involving such a wide series of neurones and muscles, is co-ordinated by a centre in the lumbo-sacral cord, called the defæcation centre. It is found, however, that if, in dogs, this portion of the spinal cord containing the centre is removed, defæcation can still proceed in a normal manner (Goltz), and the tonicity of the sphincter ani externus, which is at first lost, is recovered, even although it is a voluntary muscle and its motor nerve has been destroyed. The defæcation in this case is effected by the peristalsis of the descending and pelvic colon, and the rectum, innervated through Auerbach's plexus, which contains local cell stations. Normally, the spinal centre is under the control of the cerebrum. This control has been acquired in the course of evolution, and its autogenetic development is apparent in the child. It is well known that certain emotions, such as fear, will remove the inhibitory action exerted by the cerebrum on this centre. In Goltz's dogs, section in the mid-dorsal region of cord, cutting off voluntary control, did not interfere with defæcation, which proceeded in the normal way. If, however, in man the centre in the spinal cord is completely destroyed, the sphincter ani externus and the levatores ani become paralysed, and incontinence of fæces ensues.

The muscles and nerves involved in the act of defæcation are many. The parts of the body involved include the following:—The larynx, supplied by the vagus; the diaphragm, innervated by the phrenics; the abdominal muscles, by spinal nerves; the external sphincter ani and levatores ani, by the fourth sacral nerve. Stimulation of the hypogastric (sympathetic) nerve produces movements in the descending colon and rectum, and brings about inhibition of the sphincter ani internus.

SECTION IV.

THE CARDIO-VASCULAR SYSTEM.

CHAPTER XVI.

THE HEART.

ANATOMY.

The human heart consists of four chambers,—two auricles placed above a fibrous plate, and two ventricles below it. The plate itself is perforated so as to allow communication between the right auricle and the right ventricle, and between the left auricle and the left ventricle. The right auriculo-ventricular aperture is guarded by the three cusps of the tricuspid valve, the left by the two cusps of the mitral valve. Each valve segment is attached by chordæ tendineæ to the papillary muscles on the walls of the corresponding ventricle. The chordæ tendineæ obtain attachment not only to the margins, but also to the deep surfaces of the valve segments. Into the right auricle open the vena cava superior, the vena cava inferior, and the coronary sinus. Valves in the ordinary sense are absent at the mouths of these vessels, although septa directing the course of the blood are present. The Thebesian valve, consisting of a fold of endocardium, is found at the orifice of the coronary sinus, and the Eustachian valve, a fold of endocardium and subendocardial tissue, extends from the anterior and lower margin of the orifice of the vena cava inferior to the annulus ovalis. In the fœtus this valve serves to direct the blood entering the right auricle by the vena cava inferior through the foramen ovale into the left auricle. The four pulmonary veins open into the left auricle. The right ventricle pumps its blood into the pulmonary artery, the left into the aorta. Each of these at its origin from the heart is provided with valves. These are the semilunar valves, consisting in each case of three cusps. Each cusp resembles a small pocket, and consists of a double fold of endocardium containing fibrous tissue. At the middle of the free edge is a fibro-cartilaginous nodule, or *corpus Arantii*; whilst on either side of this two crescent-shaped areas, the *lunulæ*, remain almost free from fibrous tissue.

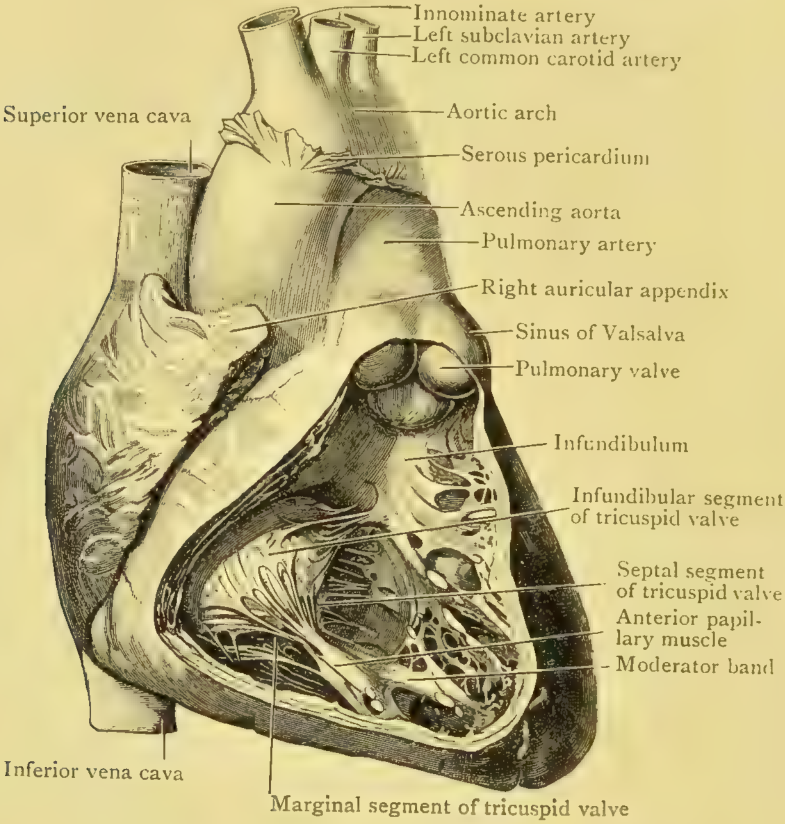

FIG. 16.—The interior of the right ventricle. (Cunningham.)

The muscle fibres composing the heart are arranged in a definite manner, the intrinsic musculature of the auricles is separated from that of the ventricles by the fibrous auriculo-ventricular rings.

The muscle fibres of the auricles are arranged in a superficial and a deep set. The superficial fibres encircle both auricles, and have a transverse course. The deep fibres have a vertical direction, arising from one side of the fibrous ring, and being inserted into the other. They are proper to each auricle.

Similarly, the ventricular muscle is composed of a superficial and a deep set of muscle bands. The deep bands are arranged in a series of three scroll-like laminæ, the distribution of which is more readily understood by a transverse section, thus:—

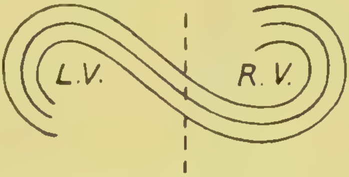

FIG. 17.—Scroll-like laminæ of the deep muscular fibres of the ventricles.

It will be seen that the deepest layer of one ventricle forms the most superficial of the other. The superficial fibres arise from the fibrous structures at the base of the heart, take a diagonal course over the heart, make a whirl round the apex, and end in the papillary muscles of the opposite side. From these they are prolonged back to the auriculo-ventricular ring via the chordæ tendineæ and the auriculo-ventricular valves. On the anterior aspect of the heart the direction of the fibres is from right to left. The walls of the auricles are about the same thickness, but the walls of the left ventricle are about four to five times as thick as those of the right ventricle. This is because the left ventricle has more work to perform; and when the resistance to the output of blood from the ventricles increases, the ventricular walls hypertrophy because of the increased work required of them. The right ventricle differs from the left, moreover, in that a strand of muscle fibres stretches across its cavity from the wall to the septum, the *moderator band*, the function of which it is to prevent over-distension of the ventricle.

Such an arrangement as described above does not provide for muscular continuity between auricles and ventricles. This is affected, however, by two fine muscular bundles: (1) the sinu-auricular bundle (Flack), (2) the auriculo-ventricular, or A–V bundle (His).

The Sinu-auricular Bundle.—The primitive vertebrate heart consists of five chambers, namely:

1. The sinus venosus, receiving the right and left ducts of Cuvier.
2. The auricular canal.

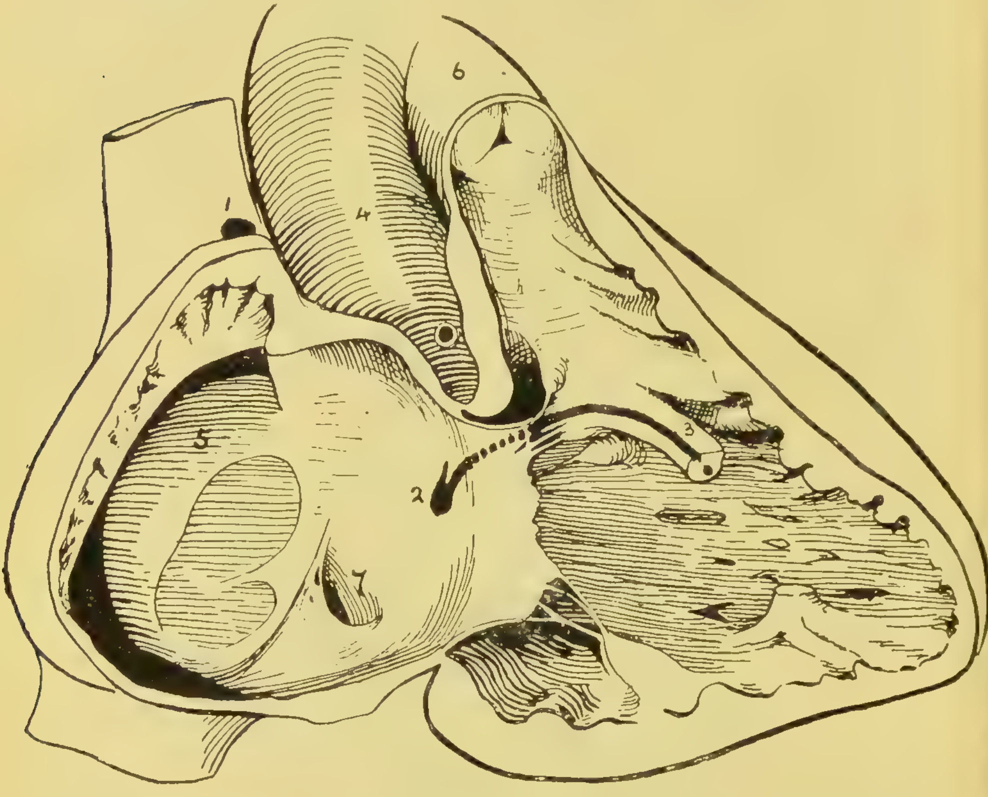

FIG. 18.—Section of a heart, exposing the septal wall of the right auricle and ventricle, and showing the position of a portion of the remains of the primitive cardiac tube. (James Mackenzie, *after* Keith.)

1. Superior vena cava above the sinu-auricular node.
2. Auriculo-ventricular node (Knoten of Tawara) from which the auriculo-ventricular bundle arises. The interrupted part represents the main bundle, and the continuation to 3 is the right division, where it is shown in the cut moderator band.
4. The aorta.
5. Right auricle below the superior caval orifice and tænia terminalis.
6. Pulmonary artery.
7. Opening of coronary sinus.

3. The auricle.
4. The ventricle.
5. The bulbus-cordis opening into the cardiac aorta.

These five portions are in muscular continuity.

The sinus venosus is that part of the heart in which the cardiac contraction commences, and it is represented in the mammalian heart by four remnants (Flack):

1. The termination of the superior vena cava (right duct of Cuvier).
2. The coronary sinus (left duct of Cuvier).
3. A stratum submerged beneath auricular tissue at the tænia terminalis.

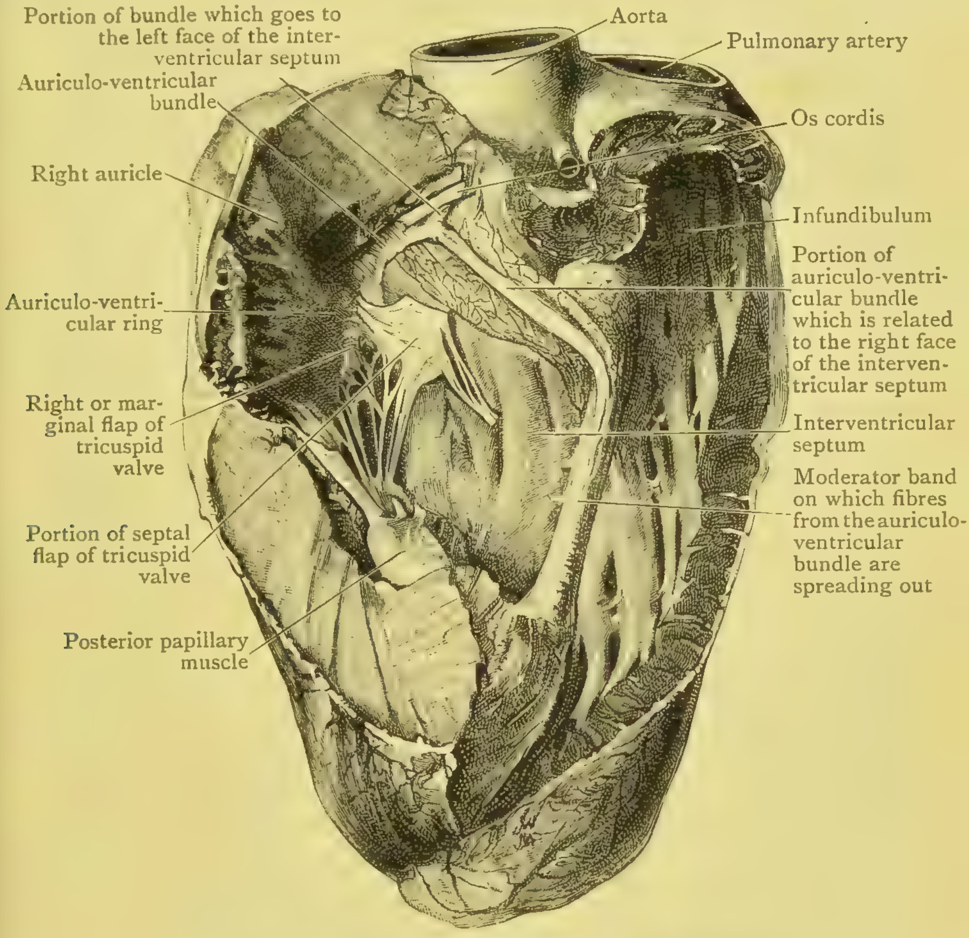
Portion of bundle which goes to the left face of the interventricular septum
Auriculo-ventricular bundle
Right auricle
Auriculo-ventricular ring
Right or marginal flap of tricuspid valve
Portion of septal flap of tricuspid valve
Posterior papillary muscle
Aorta
Pulmonary artery
Os cordis
Infundibulum
Portion of auriculo-ventricular bundle which is related to the right face of the interventricular septum
Interventricular septum
Moderator band on which fibres from the auriculo-ventricular bundle are spreading out

FIG. 19.—Dissection of the heart of a calf, by Waterston, to show the auriculo-ventricular bundle. (Cunningham.)

4. The remnants of the Thebesian and Eustachian valves.

Keith and Flack draw attention to the persistence in mammalian hearts of the remnant of primitive fibres found where the superior vena cava joins the tænia terminalis of the right auricle; this remnant is the "sinu-auricular node." From this sinu-auricular node muscular fibres pass down the inter-auricular septum to another remnant of primitive fibres placed at the base of the septum, and called the auriculo-ventricular node. The sinu-auricular node is closely connected with the vagus and sympathetic nerves and has a special arterial supply.

The Auriculo-ventricular Bundle. — The researches of Tawara have demonstrated the complex nature of this bundle. The auriculo-ventricular bundle of His commences in the auriculo-ventricular node, which lies at the base of the right side of the inter-auricular septum, just above the attachment of the middle segment of the tricuspid valve and below the fossa ovalis. The bundle courses through the auriculo-ventricular ring along the top of the interventricular septum below the pars membranacea septi, and divides into right and left septal divisions for the right and left ventricle. These fibres go to the septal groups of the papillary muscles. The terminal ramifications of the bundle arise in the papillary muscles, and pass to the ventricular walls, as Purkinje's fibres, placed in the subendothelial tissue, and on the right side they take the form of small moderator bands.

It is possible that the dominating rhythm of the heart arises at the sinu-auricular node, and that the contraction wave is conducted along the muscular fibres of the sinu-auricular and auriculo-ventricular bundles which represent that part of the vascular tube from which the heart is developed.

The coronary arteries supply the heart muscle with arterial blood. These vessels have no vasomotor nerves, and therefore are not controlled by the central nervous system. The reason for this is as follows: If the peripheral arterioles contract and the blood pressure rises, the heart has more work to do to pump the blood against the increased resistance; in these circumstances more blood traverses the coronary arteries, producing a better blood supply to the heart muscle.

HISTOLOGY OF THE HEART.

If a small piece of the ventricle of a frog is placed in a solution of 50 per cent. caustic potash, and allowed to remain there for a short time, then teased on a slide in a drop of this potash, and covered and examined in the usual way, individual muscle elements of the heart may be seen. The muscle fibres contain oval nuclei which occupy the centre, the protoplasm is seen to be slightly transversely striated, and longitudinal striations can be detected. The fibres are branched, and these branches connect with adjacent fibres. Heart muscle in the living state, however, does not consist of a number of separate cells or fibres, but of a network of cells intimately fused on all sides, forming a syncytium.[1] According to Heidenhain, the fibres forming the syncytium have many nuclei placed at regular intervals. At each pole of the nucleus is a mass of protoplasm containing basophil granules; this granular protoplasm is the sarcoplasm. Between the nuclei and the sarcoplasm, which occupy the centre of the fibres and the periphery, are the sarcostyles. These are prismatic, and exhibit longitudinal striations due to the fibres of which they are composed, and transverse striations due to the presence of singly and doubly refractile substances in the fibres. The sarcostyles constitute the contractile substance of the heart. The sarcoplasm in the interior of the fibre is continuous with a thin layer of non-fibrillated material around the periphery of the fibre. There is no sarcolemma round the cardiac muscle fibre as there is in the case of voluntary muscle. The heart muscle is originally developed from cells called myoblasts, but as development proceeds the cells become fused to form a syncytium of fibres, and the fibres contained therein pass from one fibre to another. There is therefore in this syncytium a continuity of protoplasm.

Immediately underneath the endocardium in many mammals there is a layer of beaded cells, the so-called muscle fibres of Purkinje. Each cell contains one, or sometimes two, nuclei, and exhibits at one side or the other a commencing striation. They may be regarded as embryonic cardiac muscle cells.

The auriculo-ventricular bundle of His consists of less differentiated muscle fibres than that of the rest of the cardiac muscle; the nuclei present are, however, larger.

SEQUENCE OF CONTRACTION OF THE HEART, OR CARDIAC CYCLE.

The wave of contraction extends over the mammalian heart with extraordinary rapidity. So rapid, indeed, is its progress in a freshly exposed heart that it is impossible to follow it with the naked eye. In the heart of cold-blooded animals, such as the frog and the tortoise, and in the dying mammalian heart, the sequence can, however, be readily determined. The contraction is seen to begin in the case of the frog at the sinus venosus, and in the mammal at the homologue of this—the mouths of the great veins; it is then transmitted to the auricles, and since many muscular fibres are common to both auricles, these contract practically synchronously, and in a modified peristaltic manner, though it is stated that the contraction of the right auricle precedes that of the left by a fraction of a second. The auricular contraction is known as the auricular systole, and lasts about one-tenth of a second, and the auricular systole is succeded by the ventricular contraction. In most cases there is a slight pause between the auricular and ventricular contraction; in the dog this pause amounts to one-tenth of a second, in other cases it appears to be much shorter. During this time the contraction wave is transmitted along the auriculo-ventricular bundle. The ventricles contract synchronously. On superficial examination it appears that all the fibres of the ventricles contract together, but this is not the case. The contraction wave is transmitted along the fibres from base to apex, and then from the apex along the papillary muscles to the base again, in a modified manner, and at the rate of five metres per second; in fact, the wave follows the anatomical course of the fibres as already described. Simultaneously the circular fibres contract; these constitute the driving mechanism of the heart. This is proved by an examination of the electrical variations of the beating heart. During this contraction there is not only a diminution of the cavity, but, because of the diagonal direction of the fibres, a shortening in the longitudinal direction associated with a twisting of the heart from left to right. The cavity of the heart, however, is never completely obliterated. The ventricular systole lasts about three-tenths of a second. Succeeding the ventricular systole, the heart enters into a condition of *general* diastole, which persists for four-tenths of a second. It is followed by auricular systole, and the whole cycle recommences.

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[1] A syncytium is a united mass of cells, the lines of separation between which are almost or entirely absent.

The cardiac cycle is as follows :—

CARDIAC CYCLE.

GENERAL DIASTOLE— $\frac{4}{10}$ second.		Diastolic filling of auricles and ventricles, due to suction action of ventricles, causing a negative endo-ventricular pressure. The aspiratory action of the thorax helps to fill the heart with blood. The diastolic filling causes a rise of tension in the heart cavities, which is a stimulus to contraction.
VENTRICULAR DIASTOLE persists and AURICULAR SYSTOLE occurs—$\frac{1}{10}$ second.		The auricles force more blood into the ventricles, this raises the tension in the ventricles, and also causes the flaps of the auriculo-ventricular valves to fill out.
VENTRICULAR SYSTOLE $\frac{3}{10}$ second.	1. *Compression Period*, $\frac{1}{10}$ second	All valves are closed, the endo-ventricular pressures gradually rise to overcome the pressure in the pulmonary artery and the aorta. The apex beat is produced.
	2. *Expression Period*, $\frac{2}{10}$ second	Auriculo-ventricular valves are closed, pulmonary and aortic valves open, blood expelled. Apex of heart recedes.

The whole *ventricular* diastole occupies $\frac{5}{10}$ second.

COURSE OF THE BLOOD.

During the period of general diastole the blood flows in a constant stream from the great vessels into the auricles. The pressure in the veins is small, but in the auricles and ventricles it is negative, the result of which is that the auricles and ventricles become filled with blood. The auriculo-ventricular apertures are open, and the ventricles relaxed and their cavities become distended. The effect of the auricular systole is to drive more blood onward into the ventricles; and ultimately, by producing eddies under the auriculo-ventricular valves, to bring about their closure. When the auricles contract there is a slight amount of regurgitation of blood into the superior vena cava, and this will account for the jugular pulse, which can be recorded over the jugular vein, especially if the arterial blood pressure is high. Regurgitation through the inferior vena cava is prevented by the high abdominal pressure brought about mainly by the tone of the abdominal wall. When the ventricles contract the tricuspid and mitral valves are tightened still further, and only their attachment to the chordæ tendineæ and papillary muscles prevents their flying up into the auricles, with the consequent production of regurgitation. The intraventricular pressures are then raised until they exceed the pulmonary and aortic pressures. When this is the case the semilunar valves open, not suddenly, but smoothly, and the blood is ejected through the pulmonary and aortic orifices into the pulmonary artery and the aorta. It is to be noted that it is only towards the end of ventricular systole that blood is forced into the large vessels; before this the force of the heart beat is only exerted in *getting up* the intraventricular pressures.

THE APEX BEAT.

If the bared chest of an adult, in the upright posture, is examined by inspection, it will be seen that there is a beat in the fifth intercostal space of the left side about 1 inch below the nipple, and $3\frac{1}{2}$ to 4 inches to the left of the mid-sternal line. This is the apex beat, though it is not due to the true cardiac apex, which is covered over by lung and pleura. The apex beat coincides with the compression period of ventricular systole, and only occurs where the ventricular wall touches the chest wall, *i.e.* before diminution in size of the ventricle begins. It has always been a question as to how a diminution in cardiac volume could cause a forward movement of the chest wall. The apex beat appears to depend for its occurrence upon the fact that the heart during contraction passes from a flaccid condition, in which it can make no impression upon the tense chest wall, into a hard contracted condition, and is erected and rotated forward upon its only fixed point, the cardiac base. The rotation forward is due to the curved aortic arch tending to straighten during systole. This straightening is prevented by the resistance of the chest wall against the heart, and of the vertebræ against the thoracic aorta. The pressure of the curved heart against the chest wall produces the apex beat. The position of the apex beat, however, is not constant; it varies whether the patient is lying on the right or the left side, whether he is in repose or standing erect.

CARDIAC SOUNDS.

If an ear or, better still, a stethoscope is applied to the region of the chest wall at which the apex beat occurs, it will be found that two distinct sounds are produced in the heart during the cardiac cycle. The *first sound*, as it is called, is somewhat indistinct and prolonged, and is deeper in tone. It can be heard in the isolated beating heart. Wintrich resolved it into two tones, one high and the other low. Corresponding with these two components of the sound, there are two factors concerned in its production.

1. A muscular factor, due to the contraction and the tension of the ventricular muscle, which produces the deeper tone.

2. A valvular factor, caused by the sudden tension of the auriculo-ventricular valves, and possibly the vibrations of the chordæ tendineæ and contraction of the papillary muscles. To this factor must be assigned the higher constituent-tone of the first cardiac sound.

That this is the correct explanation is proved by the fact that, in the isolated heart, the sound still continues when the fingers are held in the auriculo-ventricular orifice, or the valves held down with wire hooks. Moreover, if the auriculo-ventricular valves are suddenly thrown into tension in the dead heart, a sound is produced (Haycraft). Should a board be placed over the beating heart the sound is much intensified. Again, in pathological conditions involving these valves the first sound is modified, and it is heard most distinctly over the apex beat.

The *second sound* is shorter, more distinct, and of a higher tone, and is best heard over the second right costal cartilage near the sternum. It is due to the normally synchronous closure of the two sets of semilunar valves. If, in an animal, the semilunar valves are prevented from closing by hooking them down to the walls of the aorta, or pulmonary artery (Hope's experiment), or by the introduction of a needle down the carotid into the left ventricle, the second sound is modified. Moreover, in diseased conditions of the semilunar valves, when they are prevented from performing their normal functions, and when they allow of regurgitation of blood from the pulmonary artery into the right ventricle, or from the aorta into the left ventricle, the second sound loses its sharp distinct character, and is replaced by a regurgitant murmur. The pulmonary contribution to the second sound is most distinct in the second left interspace close to the sternum. Increased loudness of the second cardiac sound indicates an increased blood pressure either in the aorta or in the pulmonary artery.

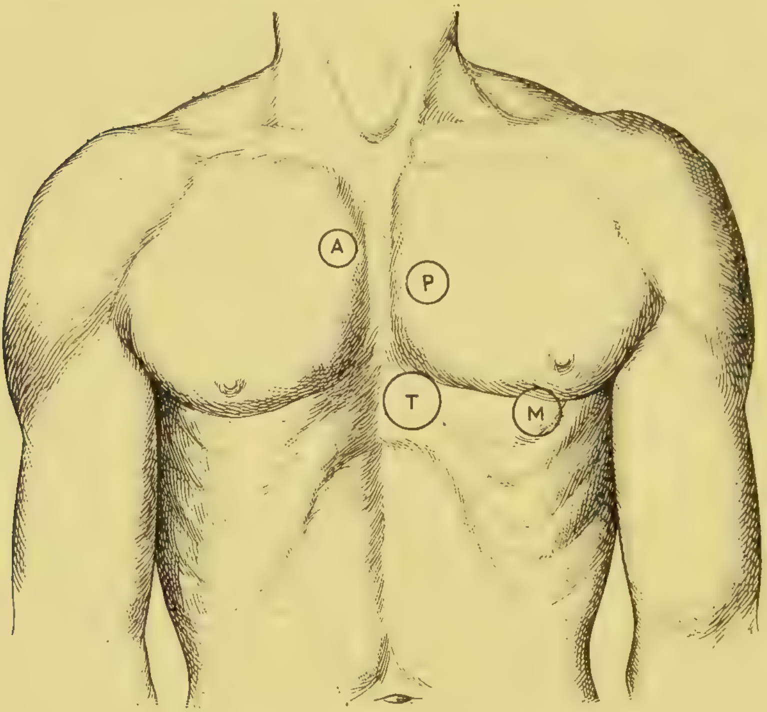

FIG. 20.—Diagram showing position of præcordial areas. (Gibson and Russell.)

A = Aortic area ; *P* = Pulmonary area ; *T* = Tricuspid area ; *M* = Mitral area.

Einthoven and Geluk have obtained graphic records of the cardiac sounds by a very ingenious method. The sounds were received by a microphone, which they connected with a capillary electrometer, and photographed the movement of the meniscus of the latter instrument upon a moving sensitised plate. At the same time they obtained records of the apex beat. Their investigations furnished complete proof of the statements above regarding the causation of the cardiac sounds.

TRACING FROM THE APEX BEAT.

If the button of a cardiograph is placed over the so-called apex beat of the heart of a man, a cardiograph tracing may be obtained. Such a tracing consists of a slight short up-stroke due to the auricular systole, a much more marked and higher up-stroke due to the ventricular systole, and then a gradual down-stroke followed by a wavy line representing general diastole. It will also be noted that the first sound of the heart occurs during two-thirds of the stage of ventricular systole, and that the second sound occurs in the earliest portion of general diastole (Fig. 21). The tracing of the apex beat is really a combined curve due to the changes in the volume and pressure of the heart; and while simple curves are easily enough interpreted, others more complicated are very difficult to read aright. Considered by itself, the tracing of the apex beat is of little value, but in conjunction with other data, it has been an important means of determining the time relations of the different phases of the heart beat in man.

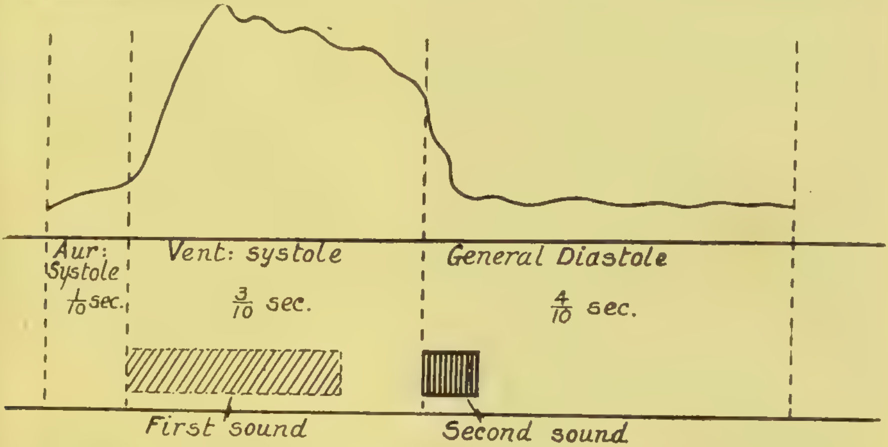

FIG. 21.—Cardiogram from the apex of human heart showing the relationship of the cardiac sounds to the cardiac cycle.

ENDO-CARDIAL PRESSURE.

The determination of the endo-cardial pressure is a matter of importance, and may be effected by a variety of methods, amongst which the following are the most important.

1. **The Use of the Cardiac Sound Sphygmoscope** (Chauveau and Marey).—A cardiac sound consists of a long metal tube something like a Eustachian catheter with an elastic bulb at the end. To determine the pressure in the right auricle the sound is passed down through the right internal jugular vein; should the left ventricular pressure be required, the sound is passed down through the left common carotid artery. It should then be connected by means of elastic tubing with a recording instrument of low inertia, such as Hürthle's recording manometer (the tubes and manometer being filled with a saturated solution of Na_2SO_4), or a Fick's C-shaped spring manometer. Should the pressure in the right auricle and the right ventricle be required simultaneously, they can be easily obtained by means of a byway sound consisting of a double tube and two bags, and so arranged that, when the instrument is passed down the internal jugular vein, one bag lies in the right auricle and the other in the right ventricle.

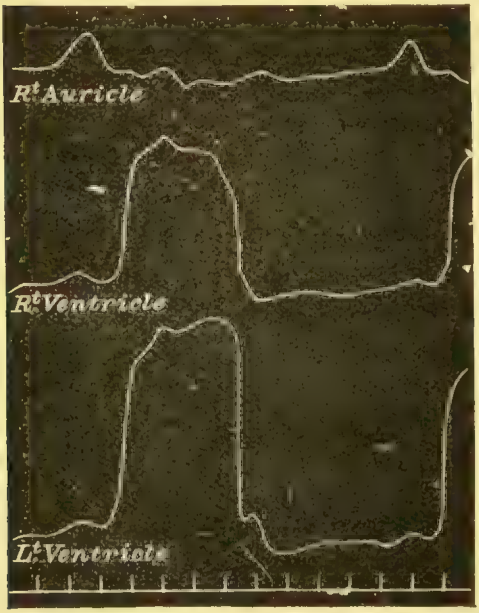

FIG. 22.—Endocardial pressure curves. (Leonard Hill, *after* Chauveau and Marey.)

2. A **hollow tube** may be passed through the chest wall into that part of the heart the pressure of which it is required to investigate, or a cannula may be passed down the internal jugular vein or carotid artery into the heart. It is connected by elastic tubing with a manometer of the type mentioned, and the whole system is filled with a solution of Na_2SO_4 or $MgSO_4$. Bayliss and Starling made use of a very delicate modification of this method. They connected the intra-cardiac cannula with a capillary tube, which they partially filled with a solution of $MgSO_4$, and sealed the top. The movements of the meniscus of the salt solution were photographed on a moving sensitised plate.

3. Should a determination of **maximum or minimum pressure**

be required, the connections are made exactly as described above, with the addition that between the cannula and the manometer is placed a maximum or minimum valve. A maximum valve is so arranged that it allows the passage of fluid from the heart and prevents its return; a minimum valve acts in the reverse manner. The valves must be in connection with the heart, and acting some little time before an observation can be made.

In the dog the figures obtained in mm. of Hg are as follows:—

	Left Ventricle.	Right Ventricle.	Right Auricle.
Maximum pressure . .	+140	+60	+20
Minimum pressure . .	-40	-15	-7

The following diagram represents the curve of intraventricular pressure (left ventricle):—

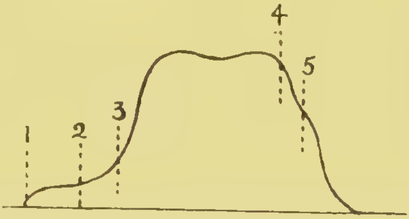

FIG. 23.—Curve of intraventricular pressure (left ventricle).

The rise in intraventricular pressure causing the curve 1 to 2 is due to blood coming into the left ventricle through the systole of the left auricle. At 2 the left ventricle is full and begins to contract, when the intraventricular pressure rises rapidly. From 2 to 3 the ventricle is getting up pressure to overcome the pressure in the aorta. Just after 3 the aortic valves open, blood enters the aorta, and continues to do so throughout the systolic plateau or top of the curve until 4, when the ventricle commences to go into diastole. The intraventricular pressure then begins to fall, it becomes less than the aortic pressure, and at 5 the aortic valves close. The intraventricular pressure then becomes negative, and in consequence blood is drawn in once more from the left auricle.

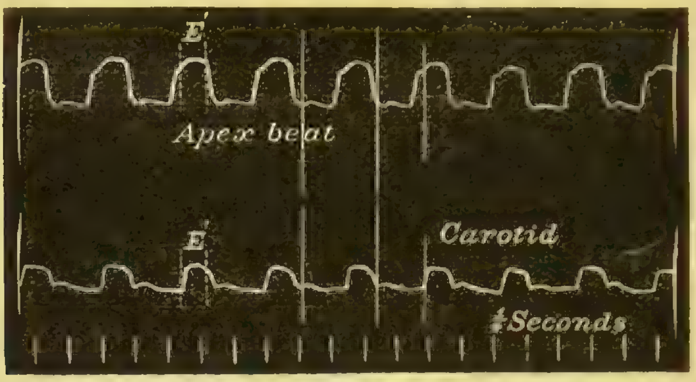

FIG. 24.—Simultaneous tracings of the apex beat and the carotid pulse, showing the "Systolic plateau" *E'* in the cardiogram during the outflow from the left ventricle. (James Mackenzie.)

CAUSE OF THE NEGATIVE INTRAVENTRICULAR PRESSURE.

The cause of the negative pressure in the heart is somewhat obscure, and its occurrence has never been satisfactorily explained. The following appear to be the chief factors in its causation :—

1. *The Elastic Rebound which succeeds the Ventricular Contraction.*—During the ventricular contraction the base of the heart, which includes the orifices of the aorta and pulmonary artery, is constricted, and this constriction is more marked at the end of systole. When the ventricles relax, the pressure of the blood in the pulmonary artery and aorta is sufficient to cause the bases of the pulmonary artery and the aorta, and likewise the base of the heart, to dilate ; this causes an increase in the capacity of the ventricles, and thus a definite negative intraventricular pressure.

2. *The Respiratory Action of the Thorax* is believed to have a share in its formation.

3. *The most important Factor appears to be the filling of the Coronary Arteries.*—The effect of ventricular systole on the coronary vessels is to empty them of blood, but with the commencement of diastole these vessels become refilled with blood from the aorta under considerable pressure ; and Benders has demonstrated that an injection of the coronary

vessels under high pressure causes diastole and a negative intraventricular pressure.

THE PERICARDIUM.

The pericardium forms a fibrous sac lined by endothelium, which is reflected over the heart. The space between the heart and pericardium is filled with pericardial fluid, a liquid having a composition which differs but little from that of normal tissue fluid. The chief function of the pericardium and the pericardial fluid is to enable the heart to contract and relax without friction. It is possible, too, that the fibrous pericardium prevents over-distension of the heart cavities.

PHYSIOLOGY OF CARDIAC MUSCLE.

2 Cardiac muscle, like other muscle, is excitable and contractile; it responds to mechanical, electrical, chemical, and thermal stimuli. It is important to note that the heart muscle responds to the chemical stimuli for muscle, such as ammonia and dilute mineral acids, but not to the chemical stimuli for nerve.

Cardiac muscle, although striated and possessing properties similar to those of ordinary voluntary striated muscle, yet has other properties which are not found in that tissue, and differs from it in certain of its physiological characteristics.

The principal differences are :—

1. The strength of the response of cardiac muscle does not vary with the strength of the stimulus. As Kronecker and Ranvier expressed it, the cardiac response is "all or nothing." Should a contraction occur in response to a given stimulus, it does not matter whether that stimulus is weak or strong, the extent of the cardiac contraction remains the same, provided that the cardiac muscle is not damaged. The smallest stimulus is either incapable of causing a contraction, or, if the heart contracts, it is a maximum response.

2. Cardiac muscle possesses a long refractory period. During the period of contraction it is comparatively inexcitable, and will not again contract until it is relaxed. This period of inexcitability, which is most marked during systole, and passes off gradually as the heart enters into the diastolic condition, has been termed by Kronecker and Starling the

refractory phase of the heart. As a consequence of this it follows:

3. That the heart muscle is incapable of entering into a condition of tetanus. In fact, if into a contracting ventricle a series of rapid electrical stimuli are passed, the cardiac rate of contraction is very often slowed. If a stimulus is applied during diastole a contraction occurs in response, this is an "extra-systole." If the stimulus is applied to the auricles or ventricle, such "extra-systole" is followed by a longer pause than normal, and this is called the "compensatory pause."

4. Cardiac muscle has a long latent period. This can be demonstrated and measured by the following method. A ligature is applied to a frog's heart between the sinus venosus and the right auricle. The auricles and ventricle cease beating. If a stimulus, *e.g.* the prick of a pin, is applied to the quiescent ventricle, it responds by a contraction preceded by a long latent period.

All the preceding phenomena Gaskell has attempted to explain on the assumption that, in cardiac muscle, the metabolic changes are slower than in ordinary voluntary muscle. That is to say, after a contraction the cardiac muscle requires a much longer period in order to rebuild the contractile material, and so place itself in a position to respond to a second stimulus.

Besides differing from ordinary striated muscle in certain characteristics, cardiac muscle possesses certain points of similarity as regards its physiological response. Should a gastrocnemius muscle of a frog be stimulated with a series of stimuli of maximal and constant strength, it is found that the first few contractions obtained are not of equal extent; they exhibit a gradually increasing variation. Bowditch, who first observed the phenomenon, applied to it the name of "treppe" or "staircase." Similarly with cardiac muscle, although in this case the staircase is even more marked. In order to demonstrate this, apply a ligature as before, and into the quiescent ventricle pass a series of effective induction shocks at intervals of 5 seconds. The second beat will be observed to be greater than the first, the third than the second, and so on, until the fifth or sixth beat, when the contraction will be observed to be maximal. A curve drawn through the ends of the recorded contractions is said to be a hyperbola. It is a moot question why muscle should show a staircase effect.

It appears that one muscle contraction exercises a stimulating effect upon subsequent contractions, and Waller suggests that this stimulating effect is due to the production of a small amount of CO_2 in the contracting muscle, which, not being removed, causes greater irritability of the muscle, and consequently more vigorous contraction. This beneficial effect of contraction is manifest in cardiac muscle only after a ligature has been applied; that is, when cardiac muscle is under abnormal conditions. Similarly to ordinary striated muscle during contraction, cardiac muscle exhibits a series of electrical changes; these will be considered in a later section.

At the end of a diastole the heart muscle is not entirely relaxed; the heart still remains in a tonic condition. Unlike the tonicity of ordinary voluntary muscle, and resembling that of the unstriated variety, the corresponding property of cardiac muscle does *not* depend upon the integrity of its nerves. The tonicity of cardiac muscle is most marked at the venous end of the heart, *i.e.* in the muscle wall of the sinus venosus; and in some hearts the tonicity of the sinus venosus undergoes rhythmic variations of diminution and intensification (Fano).

One characteristic of cardiac muscle, however, which is absent, under normal conditions, from ordinary muscle is that of rhythmicity. Cardiac muscle has an inherent tendency to contract rhythmically quite apart from a nervous mechanism. Thus, if a strip of ventricular muscle is cut in a zigzag manner, so that only narrow bridges of muscle unite the strip from end to end, it is found that such a strip will continue beating in a rhythmic manner (Engelmann). Obviously, in such a strip no nerves pass through the tissue from one to the other. Again, if this strip is suspended, and stimulated rhythmically at the other end to which the contraction usually commences, in course of time the direction of the contraction wave will take a reverse direction to that usually assumed. It is difficult to imagine that in this case there is a nervous propagation of the contraction. Such a suggestion is also negatived by the fact that the heart of a developing chick at the end of the third day contracts rhythmically, and at this time no nerves have yet grown into the heart (Pickering). Moreover, the apex of a frog's ventricle, a tissue quite independent of nerve elements, will contract rhythmically under a constant pressure (Bernstein). This property of contracting rhythmically is not equally distributed amongst the various parts of the heart; as Gaskell has shown, it has reached its highest degree of development at the sinus venosus, and gradually diminishes towards the apex. At the sinu-auricular and auriculo-ventricular junctions, however, it is higher than in the auricles and ventricle. It is quite an open question what causes this rhythmicity of the cardiac muscle, or, in other words, what the "inner stimulus" is to which it must be referred. Howell suggests that it may be due to the presence of inorganic salts in the blood. As is well known, sodium chloride is an electrolyte; that is to say, when in dilute solution it dissociates with the production of sodium ions (kations), which are charged with positive electricity, and so tend to pass to the negative pole of an electrolytic apparatus, and into chlorine ions (anions), which are charged with negative electricity, and so pass to the positive pole. In the case of the terrapin heart, Howell seems to have shown that the rhythmicity of the sinus venosus depends on the presence of potassium ions in the circulating fluid. From the sinus venosus the contraction wave is propagated by conduction along muscle fibre to the auricles, which contract in a peristaltic manner, and again from the auricles into the ventricle. Thus the beat of the heart appears to depend on the greater rhythmicity of the venous end, a condition which seems, accepting Howell's explanation, to depend on the concentration and nature of the electrolytes of the circulating fluid.

The venous end of the heart is not only susceptible to these inorganic salts, but is particularly susceptible to other stimuli, such as heat. It is found that if a cardiac tracing (cardiogram) is taken of a frog's heart, and a galvano-cautery is applied to the sinus venosus *directly*, it causes the heart to beat much more rapidly than if the galvano-cautery were applied directly to the auricles or the ventricle. Consequently the sinus end of the heart is also the region most susceptible to external stimulation. Another proof of the superior rhythmical power of the sinus venosus is afforded by the fact that in the case of death of the heart, or that part of the right auricle in the heart of the mammal which corresponds with it, it is the last portion to cease beating (*ultima moriens* Harvey).

THE ELECTRICAL VARIATION.

As has been already stated, the contraction of the heart, like the contraction of ordinary striated voluntary muscle, is accompanied by an electrical variation. Moreover, just as in the case of the stimulated gastrocnemius, these changes occur before the actual contraction of the heart, and during the time of its latent period. Contracted muscle differs from non-contracted, or from muscle which has just contracted, with regard to its electrical potential: active tissue is electro-positive to inactive tissue; that is to say, in the tissue itself a current flows from the excited to the non-excited tissue; in the external circuit the current is from the non-excited to the active part. This existence of the currents accompanying activity may be demonstrated by means of a simple preparation. A frog's heart is excised and placed upon an almost dry glass plate; its beating continues. The sciatic nerve of the frog is also exposed and removed, together with that portion of the limb including the knee-joint and below. The cut sciatic nerve is gently laid across the contracting heart of the frog, so that the cut section of the nerve is opposite the apex of the heart and the other portion of the nerve against the base of the heart. It will be seen that with every beat of the heart the frog's limb twitches. This is due to the electrical changes which occur in the heart during its latent period, and just before it contracts. Moreover, another important point is brought out by this experiment. The response of the frog's limb is a single twitch, occurring during the diastolic period of the beat immediately before the systolic phase, consequently the heart muscle contraction is not in any way of the nature of a tetanus, but is a single-muscle twitch. These electrical changes, which occur in the contracting heart of the frog, may also be demonstrated by the galvanometer, and also by the capillary electrometer. In the case of man, a tracing of the electrical variations occurring in cardiac muscle during its contraction may be obtained in a much simpler manner. The right hand, which records the electrical changes at the base of the heart, is connected with one electrode of a capillary electrometer. The changes occurring at the apex are recorded by connecting the left hand with the other electrode of the electrometer (Waller and Einthoven). The movements of the meniscus of the electrometer are photographed on a moving sensitised plate, and in this way a record of the electrical changes of the heart (an electro-cardiogram) is obtained. The curve obtained is said to exhibit triphasic variation (Bayliss and Starling). It has been shown, electrically, that the excitatory wave of the heart passes from the venous base of the ventricle to the apex, then from the apex back to the aortic base, which is connected with the large arteries (Gotch).

THE NERVOUS MECHANISM OF THE HEART.

The nerves of the heart may be divided into intrinsic and extrinsic: the intrinsic are confined within its own muscular substance; the extrinsic connect it with the central nervous system.

1. Intrinsic Mechanism of peripheral ganglia containing nerve cells which are cell stations
   - Remak's ganglion at the sinu-auricular junction (frog).
   - Bezold's ganglion on the interauricular septum (frog).
   - Bidder's ganglia in the auriculo-ventricular groove (frog).
   - Nerve cells and nerve fibres are also present in the auriculo-ventricular bundle.
2. Extrinsic Mechanism
   - Efferent nerves
     - Vagus diminishes the excitability, contractility, and conductivity, *i.e.* the anabolic nerve (Gaskell).
     - Sympathetic augmentation and acceleration, *i.e.* the katabolic nerve (Gaskell).
   - Afferent nerve
     - Depressor.

If the apex of a frog's heart is laid hold of with a pair of forceps and raised, a white crescent-shaped area will be seen lying at the junction of the sinus venosus and the right auricle. This area marks the site of the first discovered group of ganglion cells in the heart, named, after their discoverer, the ganglion of Remak. From this and through this ganglion nerve fibres pass along the interauricular septum: these septal nerves end in connection with ganglia situated on their course, the septal ganglion cells of Ludwig, or of Bezold. Finally, these septal nerves end in connection with groups of cells situated in the auriculo-ventricular groove, and named the ganglia of Bidder. There are no nerve cells in the ventricle beyond the auriculo-ventricular groove, although it is not devoid of nerve fibres. These groups of nerve cells are local cell stations, as will be shown presently. It is quite possible, however, that they also exercise a trophic influence over the cardiac muscle.

It has already been stated that cardiac muscle, particularly of the venous end of the heart, has an inherent tendency to contract rhythmically, quite apart from any nervous stimulus. At the same time, however, like all rhythmic actions, this rhythmicity is controlled and regulated by impulses which come from the central nervous system. Anatomical investigation has shown that the heart is connected with the nervous system by the vagus and the sympathetic. In the frog, however, on superficial examination only two cardiac nerves instead of four (two right and two left) can be discovered. These appear to be branches of the vagus, pass down on the superior vena cava, and enter the heart at the region of the crescent already described. Gaskell, however, by more careful searching, found that the sympathetic fibres join the vagus immediately after its passage from the cranium, and, passing down with it, are distributed to the heart. Consequently, in the case of the frog, the vagus is really not a simple vagus nerve, but a vago-sympathetic. As is well known, the heart merely represents a modified blood vessel. In the case of blood vessels which are supplied by vaso-motor nerves, no nerve ever passes directly from the nervous system to end in the plain muscular tissue of these tubes. Interposed between vessel and central nervous system is always a ganglion cell, it may be in the sympathetic chain—a lateral ganglion—or in the vessel itself—a terminal ganglion, or between the sympathetic chain and the vessel—a collateral ganglion (*vide* p. 566). By analogy one expects a similar state of affairs with the heart, and the observations of Gaskell, Langley, and Dickinson have demonstrated the truth of such a conjecture. The cardiac fibres of the vagus arise in a centre in the medulla known as the cardio-inhibitory centre; from this they pass down the vagus trunk, and through its cardiac branch to the heart. Between the medullary centre and the termination in the cardiac muscle is the interposed ganglion; in this case the ganglia of Remak, Bezold, and Bidder serve this redistributing function. The post-ganglionic fibres, the fibres of the nerve arising from the interposed ganglia, are entirely intracardiac. The fibres of the sympathetic likewise have a somewhat similar course. They arise from a nucleus—the accelerator and augmentor nucleus in the medulla (for reasons to be presently described)—and descend in the spinal cord to certain small cells in the anterior cornua of grey matter. The fibres from these cells pass out as fine medullated nerves in the third spinal nerve in the case of the frog, and in the second and third dorsal nerve, in the case of the mammal. Reaching the sympathetic cord by means of the white rami communicantes, these fibres ascend, and, branching, make synapses with the cells of the stellate ganglion (in the case of the mammal), or the ganglion immediately below the annulus of Vieussens, in the case of the frog. From these cells the sympathetic fibres are continued on to the heart as post-ganglionic fibres, in the case of the mammal, passing directly as cardiac sympathetic nerves; in the case of the frog they travel still further up the sympathetic cord, and joining the vagus at its emergence from the skull, pass, with its cardiac branch, directly to the heart.

Corresponding with this difference in the course of the impulses travelling to the heart from the central nervous system, there is a physiological difference in the effect of the stimuli passed along the different nerves. Stimulation of the vagus in an animal, *e.g.* rabbit, in which vagal and sympathetic cardiac fibres run separate and distinct courses, causes a diminution of rate, force, and tonicity of the cardiac muscle.

This may be readily shown in the case of an anæsthetised rabbit. If one vagus of this animal is exposed in the neck and tied, and the opposite vagus is also exposed and then cut, and the peripheral cut end stimulated by a series of rapidly interrupted but weak induction shocks, it is found that, after a latent period of less than one second, the heart contraction is slowed; if a stronger stimulus is used the heart may even be stopped. Gaskell found that he could stop the heart of the toad for five minutes by stimulation of the vagus by a stimulus lasting only one-eighth of that time. At the same time, he found that, instead of causing a negative variation in the electrical condition of the heart, it caused a positive variation. All these phenomena attending vagal stimulation Gaskell has interpreted to mean that cardiac inhibition is an anabolic condition; that is to say, the vagal effect is to cause a diminution of the katabolic, accompanied by an increase in the building up, or anabolic processes.

On the other hand, stimulation of the sympathetic, after a much longer latent period, produces an increase in the rate, force, and tonicity of cardiac muscle. It causes augmentation and acceleration (the rate is never more than 120 beats per minute), and it seems very probable that these separate effects are produced by the passage of impulses along different accelerator and augmentor nerve fibres. This effect may be very well shown by section of the vagi and subsequent stimulation of the medulla. In this case the medullary accelerator and augmentor centre is excited, and the result is an increase of force and rate of the heart, and there is some improvement of the conductivity of the cardiac muscle. That this effect does not depend on the vaso-constriction, which normally follows such stimulation, may be proved by section of the splanchnic nerves, when medullary excitation again produces exactly the same effects. The electrical change produced is a negative variation. All these increased variations of force, rate, tonicity, etc., and the negative electrical variation, are evidences that the sympathetic influence is one of increased activity of the katabolic processes, or a using up of stored energy.

When the vago-sympathetic of the frog is stimulated, variable effects are obtained; the results to some extent vary with the intensity of stimulation. One of the commonest effects is a condition of cardiac inhibition, which does not persist during the whole time that the stimulation lasts, but is succeeded before cessation of stimulation by a gradual return to normal contractions. Sometimes, however, the beats on return are more vigorous than usual. Such a condition, in which contraction again occurs before the stimulation ceases, is designated as "vagal escape," and the inhibition is said to cease because of the fatigue of the vagal nerve endings. On the other hand, it is quite possible that this "vagal escape" may be due to the effect of the sympathetic fibres, which were unable to act previously because of their long latent period.

In some animals, especially amongst the mammals, the heart, in addition to the efferent nerves described, possesses also an afferent nerve—*the depressor*—to be described presently.

THE PHYSIOLOGICAL ROLE OF THE CARDIAC NERVES.

The Vagus.—During life the cardio-inhibitory centre is in constant activity, exerting its inhibitory action upon the heart, or, as Howell expresses it, keeping the "brakes" on. This is shown on section of the vagi, or simply by interrupting their continuity between the medulla and the heart by the action of such an agency as cold. This tonic action of the cardio-inhibitory centre has also recently been demonstrated by Einthoven. This observer dissected out the vagus in the neck of an animal, and connected it, by means of non-polarisable electrodes, with a new instrument of similar construction to the galvanometer, in which the motion of a small mirror suspended on a quartz string gives evidence of electrical change. Such an instrument he designates the "cord galvanometer." On connecting this instrument as described, with the vagus, this observer found he obtained larger and slower waves, due to the passage of the respiratory impulses, and smaller superposed waves, due to the passage of the cardio-inhibitory impulses, which are coincident with a beat of the heart. In the new-born infant this influence of the vagus centre is not exerted, although it may easily be called into action simply by pressure applied to the top of the head.

Like all other medullary and spinal centres, the cardio-inhibitory centre is, to a certain extent, under the control of the cerebrum, and is influenced by a great many factors. Indeed, the normal tonic action of the centre must be looked upon as due to the changes arising in the cells of the centre as the result of a constant succession of afferent impulses. The influences exerted upon the cardio-inhibitory centre may be classified thus:—

1. From cerebrum.
2. Direct and through the blood.
3. Reflex.

1. There are well-authenticated cases of people who possessed the power of altering the rate of pulse at will. Again, the influence of emotional and other psychical conditions upon the heart-beat is well known. Emotional influences have been

known to so stimulate the cardio-inhibitory centre as to lead to instant and even fatal arrest of the action of the heart.

2. Pressure exerted upon the medulla will also by direct excitation of the medulla cause slowing of the heart beat, with the production of the so-called vagal beats. Changes in the 2 composition of the blood also frequently alter the rate of the heart beat via stimulation of the medulla. An important action directly upon the cardio-inhibitory centre in the medulla is seen during the changes in respiration. The heart beats 3 more rapidly during inspiration than during expiration. Even if the thorax is widely opened, and the lung changes quite unable to mechanically affect the heart, the same changes occur. It seems then that, with activity of the respiratory centre in the medulla, there is an inhibitory influence over the cardio-inhibitory centre, resulting in an increased rate of the heart beat (Fredericq).

According to Embley, chloroform acts directly upon the cardio-inhibitory centre through the blood, and causes cardiac inhibition. In animals this may be overcome by cutting the vagi; the heart recommences to contract.

3. Reflexly, cardiac inhibition can be produced by stimulation of a variety of afferent nerves. An interesting example of this is afforded by the "tapping" experiment of Goltz. This experiment is performed upon frogs, and simply involves tapping of the intestines with a light instrument, when temporary standstill of the heart is obtained. The afferent nerve in this case is the splanchnic. The brachycardia, observed in cases of peritonitis and of painful affections of certain other viscera, is likewise due to increase in vagal inhibition due to stimulation of sensory surfaces. Again, rise of arterial blood pressure in the splanchnic area reflexly causes slowing of the heart through the cardio-inhibitory centre and the vagus. Similarly marked vagal inhibition is obtained on stimulation of the central cut end of one vagus if the other vagus is intact.

The Sympathetic.—The evidence in favour of a tonic action of the cardio-inhibitory centre is definite and conclusive. In the case of the sympathetic there is no such final evidence; but the evidence, such as it is, is in favour of a tonic action exerted over the heart by the accelerator nerves. When the accelerator nerves are cut upon both sides the cardiac rate is decreased. A better proof, however, is afforded by the fact that, after section of the accelerator nerves, and the animal is left for some time, there is a persistent decrease in the frequency of the pulse (Timofeers). There seems no doubt, therefore, that a tonic action is exerted upon the heart by *both* the cardio-inhibitory and cardio-accelerator centres, although the stronger of these is undoubtedly the cardio-inhibitory. Such a balanced action is one such as would be expected, where such a high degree of delicacy of movement is required as in the heart. A similar example of antagonism that may be cited is the action of the flexors and extensors upon any particular joint.

The Depressor Nerve.—In rabbits and some other mammals (horse, pig, hare), a fine nerve courses down the neck running alongside, but dorsal (or posterior) to, the carotid artery. This nerve on dissection is seen to arise by two fine roots from the junction of the vagus with the superior (or anterior) laryngeal nerve. It is a purely afferent nerve, and stimulation of the peripheral cut end does not produce any effect. Ludwig and Lyon, investigating the effects of stimulation of the central cut end, found a great fall of arterial blood pressure gradually produced after a latent period of two or three seconds, and accompanied by a slight degree of cardiac inhibition due to the stimulation of the cardio-inhibitory centre in the medulla. Such a nerve, called, because of its action, the depressor nerve, probably exists in all mammals, but it does not take the independent course in all, which it pursues in the rabbit. In the dog and cat it is bound up with the fibres of the vagus, although it may be easily separated. From the physiological point of view it commences beneath the endothelium of the heart and commencement of the aorta, and, making connection with the medullary centres, serves as a regulator of the rate of the heart, co-ordinating this with the vascular pressure. When the endocardial pressure reaches a certain height the depressor nerve is stimulated, with the result that the blood pressure is lowered reflexly, chiefly by the opening of the flood gates of the splanchnic area. The depressor nerve does not appear to exert a tonic influence on the vaso-motor centres, for its section is not followed by a rise of blood pressure. It is said to be unfatiguable (Bayliss).

Whether the action of the depressor nerve is on a hypothetical vaso-dilator centre, or is in the direction of inhibition of the tonicity of the vaso-constrictor centre, remains a moot question; although, from the evidence at hand, the latter appears the more probable explanation of its activity.

The depressor nerve remains unique, in that it is the only afferent nerve in the body the stimulation of which is followed invariably by dilatation of the arterioles generally, but especially in the splanchnic area, with a consequent gradual fall of arterial blood pressure.

THE ACTION OF DRUGS ON THE NEURO-MUSCULAR MECHANISM OF THE HEART.

If a solution of muscarine, or physostigmine, is applied to the beating heart of a frog, the result is that the heart becomes very much slower, and finally stops in complete diastole; and, moreover, remains practically in an inexcitable condition, responding only to the strongest stimulation, or perhaps not responding at all. It is interesting, in this connection, to recall the very close chemical relationship between muscarine and a normal metabolic product of nervous activity, choline. Muscarine differs from choline solely in that it contains two atoms less of hydrogen and one atom more of oxygen.

If, to the heart, in this condition of complete diastole produced by muscarine poisoning, a dilute solution of atropine is added, after a short time, its beats recommence. Sometimes it beats more rapidly and more strongly than before. Atropine paralyses the terminations of the intracardiac vagal fibres in the muscular tissues of the heart. This is shown by stimulation of the vagus. The heart is no longer arrested. Moreover, the block must be beyond the vagal cells station, *i.e.* Remak's ganglion, because stimulation of the crescent is without effect. The inhibitory mechanism is paralysed. This antagonistic effect of atropine to muscarine is termed "physiological antagonism." On the other hand, muscarine will not produce slowing in a heart accelerated by atropine; hence this antagonism is still further qualified as an example of "unilateral antagonism."

If a weak solution of nicotine is applied to the beating heart, the first effect is a slowing, but finally a quickening is obtained. On stimulating the vagus no effect on the rate of the beat is obtained. On the other hand, stimulation of the crescent causes standstill. In this case, then, the first effect of nicotine is to cause a stimulation of the inhibitory apparatus at the region of its cell station (Remak's ganglion), an effect which is soon followed by paralysis of this same situation. It is interesting to note that, if a strong dose of nicotine is applied and acceleration obtained, strong stimulation of the crescent sometimes produces, not slowing but further acceleration. This effect is due to stimulation of the sympathetic fibres on their intracardiac course.

If digitalis is applied to a normally beating frog's heart, the systole is more pronounced whilst there is a more complete and longer diastole, provided that the drug is not in too great concentration. These changes are due to two separate effects on different parts of the neuro-muscular mechanism. The increased strength of beat is due to a direct tonic influence upon the cardiac muscle; the longer period between these beats, which allows of more complete diastole, is due to a stimulating action upon the intracardiac inhibitory mechanism. The action upon cardiac muscle is much the stronger and more important, and should too much or too strong digitalis solution be applied, the heart dies in a condition of prolonged permanent systole.

It is of interest at this point to consider the action of certain inorganic drugs upon the heart, for it has been already shown that the explanation of the property of rhythmicality in cardiac muscle stands in close relation to the existence of certain electrolytes in the blood.

The chief inorganic salts in the blood are salts of sodium, potassium, and calcium.

Immersed in a solution of 0·7 per cent. NaCl, an isolated frog's heart will retain its rhythmicality for some time, but it ultimately passes into a condition of diastolic relaxation. It is precisely the same with KCl, and if a solution of the same strength as that of NaCl is used the arrest occurs much earlier. Thus K ions and Na ions act precisely in the same manner; that is, they ultimately produce a condition of diastolic relaxation; moreover, K ions are more efficacious than those of Na. But with Ca ions it is different. A beating heart, if immersed in an isotonic solution of $CaCl_2$, ceases beating, but in a condition of systole (calcium rigor). If, however, a solution of NaCl is added, the heart beat recurs, and the strength of the contractions is increased.

These facts are made use of in the solution recommended by Ringer for perfusion, as a means by which the excised heart may be made to continue contracting for long periods. Ringer's solution consists of distilled water with sodium chloride and minute quantities of potassium and calcium chloride. Locke has added to this solution a little sodium bicarbonate and dextrose, and with this warmed (37° C.) and oxygenated solution he has successfully perfused the heart of the rabbit. This warm nutrient fluid is allowed to run through a cannula tied in the aorta of the carefully excised heart of the animal; the solution flows through the coronary arteries and, by way of the coronary sinus, eventually gets into the right auricle, whence it escapes through an opening previously made in the right auricular wall.

In this way Locke has been able to keep the rabbit's heart beating for many hours, and in some instances for days. During this time it has been found that some of the dextrose is used up by the heart muscle.

STANNIUS' EXPERIMENTS ON THE FROG'S HEART.

Stannius' experiments consist in the application of ligatures to the frog's heart. The *first* Stannius ligature is placed around the sinu-auricular groove or the cardiac crescent, and should be applied rapidly and forcibly and during systole. The auricles and ventricle usually cease beating, and remain in a condition of relaxation, the sinus continues to beat with unaltered rhythm. Two explanations of this result have been offered—

1. That the application of the ligature acts as a mechanical block in the course of the modified peristaltic wave.

2. That the ligature mechanically stimulates the extrinsic vagal terminals as they end round the cells of Remak's ganglion, so causing a nervous inhibition of the heart beat.

Should the heart be left to itself, the ventricle may begin to beat, though with an altered rhythm. This is due to the rhythmicity of the auriculo-ventricular junction (see section on Physiology of Cardiac Muscle).

The *second* Stannius ligature is applied somewhat slowly and gently between the auricles and ventricle in the auriculo-ventricular groove. The result is the same as if the ventricle was cut off from the heart after application of the first Stannius ligature. The auricles remain quiescent, but the ventricle commences contracting with a rhythm quite different from that of the sinus venosus. Two explanations of this have been offered—

1. That the second ligature acts mechanically, merely as a stimulus to the rhythmic tissue of the auriculo-ventricular ring. This seems the more rational explanation, for, as previously mentioned, the ventricle may commence to beat even without any external stimulus; or, should it not beat, the application of any other mechanical stimulus, such as a pin-prick, is quite sufficient to initiate contractions.

2. That the application of the second ligature cuts off the inhibitory influences of the former. Consequently the ventricle recommences its contractions.

With regard to the first ligature, the mechanical theory is probably the correct one. For in an atropinised frog's heart contracting rapidly the first ligature, if properly applied, causes arrest of the auricles and ventricle. If the second view were correct it would be difficult to understand how, after paralysis of the vagal terminations in the cardiac muscle, stimulation of Remak's ganglion could cause arrest.

THEORIES OF THE HEART BEAT.

It has been shown that cardiac muscle contracts rhythmically and automatically, quite independently of the central nervous system; but with regard to this rhythmicality there exist two views, which may be concisely expressed as the "neurogenic" and "myogenic" theories of the heart beat.

The **neurogenic theory** supposes that the internal stimulus to the heart beat *arises* within the nerve cells which are present at the venous end of the heart, and that the *excitatory* wave is conducted by nerves. There is very little to support such a view, but the chief facts are the following:—

1. In the heart of the king crab (Limulus) the nerves take a longitudinal course upon the surface of that organ. Carlson has removed these nerves, and on doing so found that the heart no longer contracts. This has been interpreted as meaning that the contraction of the heart depends upon the nerves in it. Obviously it does in the case of Limulus, but the experiments upon this animal cannot be applied to the frog's heart, still less to the mammalian. The heart muscle of Limulus does not differ in its properties from ordinary

skeletal muscle. It can be tetanised, it has no refractory phase, nor does it follow the "all or nothing" law.

2. According to the investigations of Kronecker and Schmey, puncture of a particular point on the intraventricular septum always brings about fibrillary contraction of the ventricular muscle. This they interpret as meaning that, at that particular spot, there is a special nerve centre co-ordinating the contractions of the whole ventricle. As MacWilliams has demonstrated, however, no nerve centre can be shown histologically at this point, and, moreover, the heart may frequently recover from this condition and again exhibit normal co-ordinated contractions. Kronecker and Schmey's observations, though interesting, cannot be brought forward as proving that the beat of the heart is due to a neurogenic agency.

The **myogenic theory** supposes that the heart muscle itself possesses the property of automatic rhythmicality, and that this property, as already stated, is most marked at the venous end of the heart, and at the sinu-auricular and auriculo-ventricular junctions. The contraction wave is generated at the venous end of the heart in the muscle, and, in virtue of the conductivity of cardiac muscle, spreads over the muscle tissue of the auricles, and thence over the ventricles. In other words, the contraction wave *commences* in muscle and is *conducted* by muscle. The muscular continuity of the auricles and ventricles is brought about, as already indicated, by the auriculo-ventricular bundle of His. This auriculo-ventricular bundle contains both ganglion cells and nerve fibres, and serves for the passage of the wave of conduction from the auricular to the ventricular musculature. This has been shown by the experiments of Erlanger. This observer experimented with dogs. In these animals he found that, by compression of the animal's ventricular bundle, he could obtain all stages of heart block. He obtained an increase of the intersystolic pause between auricular and ventricular systole; then, by increasing the pressure of the clamp, he obtained—

1. An occasional ventricular systole.
2. Regularly recurring ventricular silences; thus one silence in ten, nine, eight, etc. auricular beats.
3. A condition in which the rhythm of auricles to ventricles was as two to one; ending,

4. Finally, in complete heart block. When complete heart block is established, an independent slow rate of ventricular beat is usually established. It is peculiar that, with a complete heart block thus produced, excitation of the vagus has no effect upon the contraction of the ventricles (although it has the usual effect upon the auricles); while stimulation of the sympathetic causes increase of both auricular and ventricular rates.

The rate of conduction along this strand of relatively undifferentiated cardiac muscle tissue, the auriculo-ventricular bundle of His, is also less than over the more differentiated cardiac muscle. In the latter case it has already been stated as travelling five metres per second (Wallis); but in the dog, with an interval between auricular and ventricular systole of one-tenth second, in which the length of the auriculo-ventricular bundle is only about 15 mm., the rate of conduction along this bundle can only occur at 15 cms. per second.

In favour of the theory that the wave of contraction is conducted along muscle (myodromic), and is myogenic in origin and not neurogenic, the following points which support the theory of independent cardiac rhythmicity must be kept in mind :—

1. Engelmann's observation on the zigzag strip of ventricular muscle. The ventricle of the frog may be so cut that all conducting nerves are cut, yet the wave of contraction passes (*vide* p. 185).

2. Bernstein's observations on the nerveless apex of the frog's ventricle (*vide* p. 188).

3. Gaskell showed that if the coronary nerve of the heart of the tortoise is sectioned the muscular influence passes along, whereas if the muscle is clamped allorrhythmia is produced. Two auricular contractions occur to one ventricular, three auricular contractions to one ventricular, etc., according to the tightness of the clamp.

4. His's observation that the embryonic heart beats when no ganglion cells have invaded the heart.

5. Pickering's observations on the heart of the embryonic chick, that drugs like atropine, which act upon nerves, have no action upon the embryo chick's heart. The conclusion drawn is that the embryo heart is nerveless.

The balance of evidence is certainly in favour of the myogenic theory.

HEART BLOCK.

It has already been shown that a condition of heart block may be produced in one of two ways, either by the application of the first Stannius ligature between the sinus venosus and the right auricle, and the clamping of the auriculo-ventricular bundle. In both cases the disturbance of the rate and rhythm of the heart beat may be attributed to impairment of the conductivity of its neuro-muscular mechanism, whether neurogenic or myogenic,—in one case across the sinu-auricular bundle, in the other along the bundle of His. In both cases the immediate stoppage of the rhythm of the ventricular beat is followed by the establishment of a second rhythm independent of, and frequently bearing no relation to, the rate of sinus or sinu-auricular contraction. In the lower animals (tortoise), as well as in the mammalia, a condition of partial heart block may be readily established by the application of Gaskell's heart clamp in the auriculo-ventricular groove. The conductivity may be so impaired that a ventricular beat no longer succeeds an auricular beat, and that only one ventricular contraction may be obtained in response to every two auricular beats. If the pressure is still further increased, only one ventricular beat may be obtained to every three auricular contractions. Further increase of pressure may lead to complete rupture of all relationship between the auricular and ventricular contractions. As already mentioned, section of the auriculo-ventricular bundle brings about complete heart block.

In pathological conditions of the human heart, both conditions of partial and complete heart block may be met; and it may well be that, in a certain proportion of cases, lesion of the auriculo-ventricular bundle (syphilitic disease) has caused the defective conductivity from auricles to ventricles. Occasionally, too, it may be brought about by vagus stimulation following the administration of digitalis or helleborin. The rate of auricular contraction may have dropped to fifty-six, as observed by taking a tracing over the jugular vein; whilst, from apex observation, the rate of contraction of the ventricles may have fallen to 28. In these cases an improvement may often be brought about in the conductivity of the auriculo-ventricular bundle by the administration of atropine.

In the mammalian heart there may also be a block between the superior vena cava and the right auricle comparable with the sinu-auricular block of the frog's or tortoise's heart.

Heart block is one of the factors in the Stokes-Adams syndrome, in which the patient has a slow pulse of 30 or 40 beats per minute with attacks of giddiness, and a visible auricular impulse in the veins of the neck.

The Output of the Heart.—A simple form of cardiometer, or heart plethysmograph, was devised by the late Harold Barnard for use upon the heart of a mammal such as a cat or small dog. The instrument consists of a stout indiarubber ball, in one portion of which a circular orifice is cut and enlarged by two or more slits. A small glass tube is firmly fixed into that portion of the ball which is opposite the circular orifice. The animal is fully anæsthetised, the thorax opened, and the pericardium exposed. Artificial respiration is kept up by means of a tube previously introduced into the trachea. The pericardium is opened by means of a crucial incision and four pericardial flaps are obtained. The ball is now carefully applied over the heart and the four pericardial flaps tied down over the ball around the glass tube. The apparatus is made airtight by previously placing vaseline around the orifice in the ball. In this way the ball takes the place of the pericardium. The glass tube is connected by short indiarubber tubing with a Marey's tambour, the writing point attached to the lever of the tambour is adjusted to write against a moving blackened surface.

When the heart goes into systole, air is drawn into the ball from the tambour; when the heart goes into diastole, air is driven from the cardiometer into the tambour. The variations in the movements of the lever of the tambour correspond with the volume of blood expelled from the heart during systole, and drawn into the heart during diastole. If the instrument is calibrated the exact volume of blood expelled from the heart at each systole may be ascertained.

The Work of the Heart.—The potential energy of the heart is utilised in ejecting from the heart at each systole a definite volume of blood against a definite resistance, and imparting to it a definite velocity. The work done by the left side of the heart may be expressed by the equation $W = V.P.' + \frac{1}{2}m\ v^2$,

Where V = volume of blood put out by the heart at each systole measured in cubic centimetres; this is calculated to be about 100 c.c.

P = the main aortic pressure; this is approximately 120 mm. of Hg.

m = the mass of the blood.

v = the velocity imparted to the mass of blood; this is nearly five times greater than the mean velocity of the blood in the aorta.

The work done by the right side of the heart is about one-third that done by the left side.

In this way it has been calculated that the total work of the heart per diem is equal to about 23,880 kilogramme-metres. As Waller expresses it, the work done by the human heart in the day is equal to that done by an able-bodied labourer working hard for two hours.[1]

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[1] "John Hunter described the tricuspid valve as being barely sufficient to close the tricuspid orifice, and the experiments and clinical observations of King and Gibson have shown how easy it is to induce tricuspid regurgitation. A well-acting heart possesses the power of altering the size of its chambers in accordance with the calls made in its work, apart altogether from its systole and diastole. This is due to the muscular walls possessing the function of tonicity, a function which enables the heart to alter the size of its chambers in order to accommodate itself to the exigencies of life. When we consider the extremely varied amount of effort which the heart is called upon to expend, it will be easy to understand that a physiological dilatation may often be called into operation. If, then, the tricuspid valves are barely competent, it is readily understood that a slight degree of physiological dilatation will render them incompetent.

"Moreover, the auricles are specially constructed to meet this incompetence. The older physiologists were wont to describe the main function of the auricles as being that of reservoirs, capable of varying their contents to meet the varying circumstances of cardiac activity. This is probably their most important function, for in many cases the work of the heart can be carried on efficiently when the auricles cease to act as contracting chambers" (James Mackenzie, *Oliver-Sharpey Lectures*).

CHAPTER XVII.

THE CIRCULATORY SYSTEM.

Course of the Circulation.—The right auricle receives the venous blood as it returns from the tissues, and transmits it to the right ventricle. The function of the right ventricle is to pump the venous blood through the pulmonary arteries into the lung capillaries, where the venous blood becomes oxygenated. The oxygenated blood returns by the pulmonary veins to the left auricle, and the arterial blood is then received into the left ventricle. The left ventricle pumps the arterial blood through the large arteries, the small arteries, and the arterioles into the systemic capillaries. For the most part between the capillaries and the tissues is the tissue fluid, and across this the tissues acquire the oxygen from the arterial blood, and return carbon-dioxide to the blood in the capillaries. The blood which leaves the tissues is venous. The venous blood returns from the capillaries through the small veins into the larger veins, and the largest veins pour the blood back into the right auricle. It will thus be seen that the right side of the heart is occupied with the pulmonary circulation, and the left side of the heart with the systemic circulation. The blood, returning from the stomach, the small, and the greater part of the large intestine, returns by the venules which open into the superior and inferior mesenteric veins. These join with the splenic vein to form the portal vein, and the blood then traverses the capillaries and the sinusoids of the liver. From these capillaries the blood is collected into the hepatic veins, which return it into the inferior vena cava. The circulatory system possesses two regulating reservoirs. The intralobular veins, the lobular blood capillaries and sinusoids of the liver act as a reservoir for the systemic circulation, so that the right side of the heart may acquire a greater or less volume of blood from the large veins without altering the systemic pressure. The capillaries of the lungs act as a reservoir for the left side of the heart, so that blood may accumulate there, if for any reason the output of the left side of the heart diminishes.

THE FŒTAL CIRCULATION.—The arterial blood returns from the placenta by the umbilical vein, which traverses the umbilicus and travels up to the liver. A small portion of this blood traverses the liver through the venæ advehentes which break up into capillaries, from which the blood is collected by the venæ revehentes, which open into the hepatic vein and thence into the inferior vena cava. The greater portion of the blood, however, which comes to the fœtus by the umbilical vein traverses the ductus venosus in the longitudinal fissure of the liver, which opens straightway into the inferior vena cava. The arterial blood returning from the placenta gets into the right auricle. The blood is driven from the right auricle into the left auricle through the foramen ovale. From the left auricle this arterial blood gets into the left ventricle, and from the left ventricle it is driven into the aorta, and goes then chiefly to the head and neck, which at this time develop somewhat rapidly. The blood, which has lost a portion of its oxygen, returns from the head and neck by the jugular veins, thence through the innominate veins into the superior vena cava. This blood is poured into the right auricle, and the particular arrangement of the Eustachian valve in the right auricle prevents any appreciable mixture of this blood with that which comes in by the inferior vena cava. The blood, which has arrived by the superior vena cava, now goes from the right auricle into the right ventricle, from the right ventricle it is propelled into the pulmonary artery. At this time, as the lungs have not expanded, there is an impediment to the blood circulating through the pulmonary vessels, but the blood passes from the pulmonary artery by the ductus arteriosus into the descending part of the arch of the aorta, and so down the aorta to be distributed to the developing tissues. The bulk of the blood flows through the internal iliac arteries into the hypogastric arteries, which run alongside the allantois to the umbilicus, and these two arteries traverse the umbilical cord as the umbilical arteries. These convey the venous blood to the placenta, where the blood becomes again oxygenated. It is obvious from this that, at birth, when the umbilical cord is tied, very important changes must take place in the circulation of the child. The blood clots in the umbilical vein between the ligature, which has been applied, and the liver, and also in the ductus venosus. The blood clot becomes organised, and the umbilical vein and the ductus venous therefore obliterated. As respiration commences blood is induced to traverse the pulmonary arteries, and then returns to the heart by the pulmonary veins; this raises the pressure of the blood in the left auricle, and causes the valve over the foramen ovale to commence to close down. At the same time the blood in the ductus arteriosus clots, the clot organises, and the ductus arteriosus becomes a fibrous cord. The blood in the hypogastric arteries from the top of the bladder to the ligature round the umbilical cord also clots; the clots organise, and the hypogastric arteries gradually become obliterated.

Factors of the Circulation.—The function of the heart is to empty the veins and fill the arteries. It does this by its regular contractions, and is aided in this function by the cardiac valves, which prevent the regurgitation of blood. The large arteries, as the aorta, contain in their tunica media a large amount of yellow elastic tissue; the full arteries are, by means of this, able to receive a further quantity of blood from the heart. Each time the left ventricle contracts it forces 100 c.c. of blood into the already full arterial system. The distended large arteries then recoil upon the contained blood, causing such a constant pressure to be exerted on the blood that what would be an intermittent stream is converted into a continuous onward stream of blood. The arteries are not only conducting tubes, but they exert a propulsive force assisting the heart in driving the blood into the capillaries, and inducing a continuous flow. The large arteries, because of the large amount of yellow elastic tissue which they contain, help to maintain a "head of pressure" sufficient to allow any portion of the body to become flushed with blood when the arterioles dilate. The arterioles have in their middle coats a large amount of plain muscle which is directly influenced by the vaso-motor nerves, and in this way the arterioles act as a form of resistance to the blood stream, and so keep up and regulate the arterial blood pressure. At the same time they regulate the amount of blood traversing the capillaries of the body. The portal vein is also supplied by vaso-motor nerves, and by their means the amount of blood supplied to the liver is under control of the nervous system. On the other hand, the pulmonary arteries are said to be without vaso-motor nerves. The amount of blood traversing the lungs is mainly dependent upon the respiratory movements. The chief use of the plain muscle in the walls of the arteries and arterioles is to keep up the tonus of the vessels; at the same time, it is useful in stopping hæmorrhage, for if an artery is cut through, the damaged surfaces first *contract*, so that the bleeding orifice becomes smaller, then the coats *retract* within the tunica adventitia, the blood which lies between the retracted ends and the outer coat of the vessel *clots*. It is important to remember that the muscular wall of the arterioles has a certain amount of independent action apart from vaso-motor nerves. It contracts when exposed to cold or to great heat. Ergot causes the muscular coat to contract, while nitrates cause the muscular coat of the arterioles to relax. The function of the thin-walled capillaries is to supply the tissue fluid which is found in the extravascular spaces, and it is this fluid which bathes the tissues and supplies them with nutrition, and to a certain extent with oxygen. The function of the veins is to return the blood from the capillaries to the heart. The onward circulation of the veins in the extremities is, to some extent, dependent upon the contraction of the voluntary muscles around the veins. When the muscles contract, they squeeze the blood in the veins onwards towards the heart; a backward flow is prevented by the presence of small semilunar valves. These are placed in the veins, as a rule, opposite the opening of the venous tributaries. The veins of the lower extremity are plentifully supplied with these valves.

BLOOD PRESSURE

By the blood pressure is meant the pressure that the blood exerts against the wall of the vessel in which it is contained. The term blood pressure, therefore, will include endocardial pressure, arterial blood pressure, capillary blood pressure, and venous blood pressure. The following diagram represents the height of blood pressure throughout the systemic vascular system—

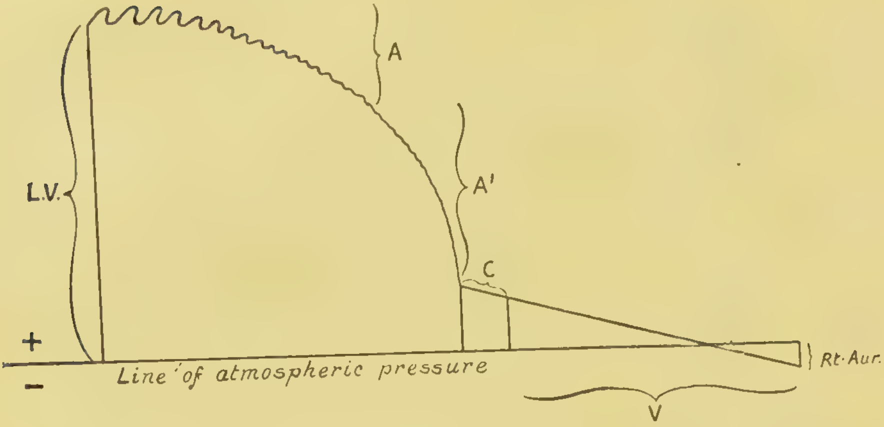

FIG. 25.—Diagram to represent the relative heights of the blood pressure in the vessels.

L.V. Blood pressure highest in left ventricle just before the aortic valves open.
A. Arterial blood pressure, oscillations due to cardiac systole and diastole.
A'. Extensive fall of blood pressure in the arterioles.
C. Capillary blood pressure.
V. Venous blood pressure rises during expiration, falls during inspiration.
Rt. Aur. A minus pressure.

The arterial blood pressure will be considered first. The factors which produce and help to maintain the arterial blood pressure are as follows :—

1. The force of the contraction of the left ventricle.

2. The volume of blood which it pumps out into the already full arteries (the left ventricle puts out three ounces at each contraction). This factor is not of so much importance as might be expected, for there are compensating mechanisms. If arterial hæmorrhage occurs, the arterial blood pressure falls, but is quickly restored, because the blood vessels contract and accommodate themselves to the blood which they contain; and, moreover, fluid is withdrawn from the tissues; the converse of this is also true.

3. The perfect aortic semilunar valves, which prevent regurgitation of the blood into the left ventricle when it goes into diastole.

4. The elastic resiliency of the middle coats of the large arteries. These contain much yellow elastic tissue, which gives when more blood is received from the heart into the already full arteries and then recoils. It is this recoil which converts an intermittent into a continuous force, and produces a continuous onflow of the blood in the vessels.

5. The peripheral resistance exerted by the muscular wall

of the arterioles, which are especially controlled by the vaso-motor nerves. It is this peripheral resistance which mainly regulates the diastolic pressure.

6. The increased surface over which the blood flows through the capillaries. It has been estimated that the capillaries together make up an area about 800 times the sectional area of the mouth of the aorta.

7. The tension of the extra-vascular tissues, *i.e.* the elastic pressure exerted upon the blood vessels from without and the atmospheric pressure. Crile found that, by enclosing an individual in a pneumatic rubber suit into which air can be pumped, the blood pressure may be controlled to the extent of 25 to 60 mm. of Hg.

MEASUREMENT OF THE ARTERIAL BLOOD PRESSURE.

1. **In an animal.**—The arterial blood pressure of an animal is usually registered by Ludwig's kymograph. The method is as follows:—The animal, such as a cat, having been anæsthetised, an artery, the common carotid or the femoral, is exposed. A ligature is placed around the distal portion. A small clamp is placed on the proximal portion, leaving about three-quarters of an inch between the ligature and the clamp. A longitudinal incision is made in this piece of the artery, and a T-shaped glass cannula with a small bulb in the centre (Franck's) is introduced and securely tied in. On the limb of the cannula opposite that inserted into the artery is a piece of soft rubber tubing which is kept clamped. The middle portion of the cannula is connected by a piece of flexible metal tubing, or very thick indiarubber tubing, to the proximal limb of a U-shaped mercurial manometer. Between the cannula and the manometer there is a side-way and a tube, by which a neutral saline solution (half saturated solution of sodium sulphate) may be introduced, so that when the clamp is released from the artery the blood comes in contact with the salt solution in the cannula, and the pressure of the blood is thus transmitted through the salt solution to the Hg. It is found advisable to raise the pressure of the salt solution above the anticipated arterial blood pressure. This precaution prevents the blood getting into the T-shaped

cannula, and therefore prevents the blood clotting. If during the experiment the blood clots in the cannula, the clot may be washed out by first clamping the artery; and, secondly, by forcing some of the salt solution into the cannula, the clot and the fluid escaping at the opposite extremity of the T-shaped cannula to that which is in the artery, the clamp being previously removed from the rubber tube. On the mercury in the distal limb of the U-shaped manometer is a float with a writing point which is placed against a revolving

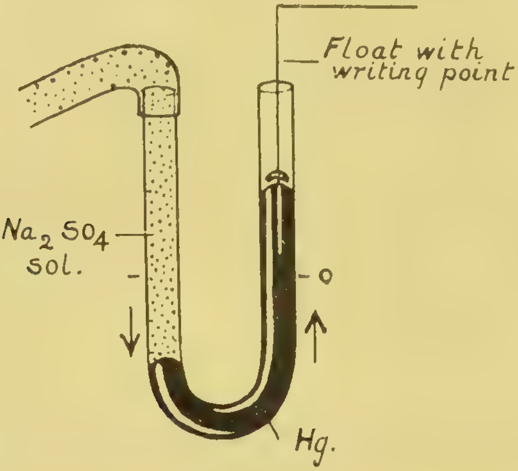

FIG. 26.—Mercurial manometer.

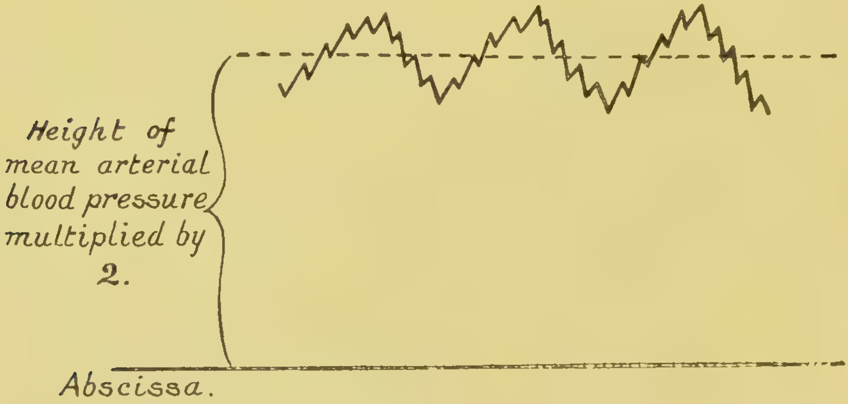

FIG. 27.—Diagram of a tracing of arterial blood pressure. The large waves are due to respiratory movements; arterial blood pressure is highest just *after* the end of inspiration, lowest just *after* the end of expiration (*vide* Fig. 51). Smaller waves are due to cardiac systole and diastole.

blackened surface, and in this way the arterial blood pressure tracing may be obtained. As the mercury in the proximal limb of the U-shaped tube is forced down, so that in the distal limb of the U-shaped tube is forced up, and the resulting pressure obtained is the difference between the level of the mercury in the proximal limb and the level of the mercury in the distal limb. An arterial blood pressure tracing shows two sets of waves, the larger waves due to respiratory movements; with inspiration the arterial blood pressure rises, and with expiration the arterial blood pressure falls. On these larger waves are seen the heart beats, a small up-stroke with cardiac systole, and a small down-stroke with diastole. As a rule there are more heart beats during inspiration than during expiration; that is, there are more beats on the up-stroke than on the down-stroke.

Experiments upon Blood Pressure.—If one vagus is tied, and a double ligature applied to the opposite one, which is then cut between the ligatures, and the peripheral cut end stimulated by rapidly interrupted induction shocks (weak), the heart of the animal will be slowed. If the stimulus is a strong one, the heart may be, for the time being, completely inhibited; the result is a sudden fall of arterial blood pressure. If the stimulus is removed, with one or two heart beats the blood pressure curve rises, and for a short time it is frequently found to be somewhat higher than before. This effect may be due to an increased volume of blood pumped into the arteries, it having accumulated on the venous side of the circulation during cardiac inhibition. The blood pressure curve rapidly regains its former normal level. If the animal whose arterial blood pressure is being recorded has a separate depressor nerve, it may be exposed, cut, and the upper cut end stimulated; the result of this is that afferent impulses travel up to the vaso-motor centre, the result of which is to inhibit the activity of the tonically acting vaso-constrictor part of the vaso-motor centre or possibly to increase the activity of the vaso-dilator part of the centre. Fewer or weaker impulses pass down the spinal cord to the peripheral arterioles in the splanchnic area, the result of which is some relaxation in their muscle tone, the arterioles dilate, and the arterial blood pressure gradually falls. This is known as a *depressor* effect, and the term applies to the arterial blood pressure. A similar effect *may* follow the stimulation of the upper cut end of the vagus, for those animals with no distinct depressor nerves have depressor fibres in the vagi. If, on the other hand, any large mixed nerve, such as the sciatic, is cut, or the cords of the brachial plexus, or the vagus itself, and the upper cut end is stimulated, afferent impulses travel up to the vaso-constrictor part of the vaso-motor centre. The result of these impulses is to increase the activity of the vaso-constrictor part of this centre; stronger impulses descend the spinal cord, and travel to the arterioles in the splanchnic area, these become constricted, and the arterial blood pressure gradually rises; this is a *pressor* effect, and the term applies to the blood pressure.

If a solution of the extract of the *medullary portion* of the suprarenal capsule—that is, a solution which contains the active principle of the gland (epinephrin, suprarenin, adrenalin)—is injected into the jugular vein of the animal, the arterial blood pressure of which is being recorded, there follows a gradual rise of arterial blood pressure. This is due to the suprarenal extract stimulating the vaso-motor nerve terminals in the walls of the arterioles, which then become constricted. The arterial blood pressure curve, however, soon returns to normal. If suprarenal extract is injected first, stimulation of the upper cut end of the depressor nerve fails to cause vaso-dilatation. If a solution of choline, a decomposition product of the lipoid lecithin, is injected into the jugular vein of the animal, it will produce a gradual fall of arterial blood pressure; this is chiefly due to vaso-dilatation of the splanchnic peripheral arterioles. Most animal extracts cause a slight fall of arterial blood pressure when injected into the jugular vein.

2. **In man.**—This may be done with a Riva-Rocci sphygmometer. The individual whose blood pressure is about to be recorded should be placed in such a position that his heart, the artery the blood pressure of which is to be determined, and the manometer are at the same level. It is usual to record the pressure in the brachial artery. The indiarubber bag of the instrument should be wrapped round the bared arm, the metal covering of the bag should then be adjusted, and firmly strapped in position. The indiarubber tube leading from the bag is then adjusted to the proximal limb of the U-shaped manometer which contains mercury. The experimenter places the index-finger of his left hand over the radial pulse of the subject, and with his right hand he

compresses the syringe and so drives air into the indiarubber tube and the indiarubber bag around the individual's arm. The pressure of the air in the bag around the arm is recorded by movement of the mercury from the proximal to the distal limb of the manometer. The operator keeps on pressing the syringe until oscillatory movements are seen at the surface of the mercury in the distal limb of the manometer; the mean point of maximum oscillations registers the diastolic pressure. If the pressure in the bag is still further increased, the oscillations diminish in amplitude and finally disappear, and at this point the pulse can no longer be felt at the wrist. The height of the mercury supported then registers the amount of systolic pressure. It will then be noted that the mercury has descended in the proximal limb of the manometer, and has ascended in the distal limb of the manometer; the difference between the two mercurial levels will be the blood pressure of the brachial artery. The normal systolic pressure in man is about 120 mm. Hg, and the diastolic pressure about 100 mm. Hg. In women the pressures are about 10 per cent. less. In children the systolic pressure may be as low as 90 mm. Hg, with a diastolic pressure of about 80 mm. Hg (R. Hutchison).

The blood pressure in the radial artery may be estimated by the sphygmometer (Hill and Barnard). This instrument consists of a glass tube graduated in mm. of Hg. At one end is an indiarubber bag, at the other a stop-cock. The indiarubber bag contains black ink, the stop-cock is opened, and the indiarubber bag pressed so that the black ink is forced up the tube as far as the mark O, the stop-cock is closed so that between the mark O and the stop-cock is air. The sphygmometer is then applied over the radial pulse, and kept in position by a clamp. It is then gradually pressed down over the radial artery, and the ink is gradually forced up the tube. The pulsations from the artery are transmitted to the indiarubber bag, so that during cardiac systole the ink is forced up; with diastole the ink returns. The pressure of the sphygmometer is so adjusted that the largest oscillations are obtained. The mean is then noted, and this gives the mean radial blood pressure. Suppose, for instance, that the highest rise of the ink stands at 120, and that the return fall goes back to 100, the mean radial blood pressure will be 110 mm. Hg.

The Blood Pressure in Man in MM. of Hg.

Large arteries	+140 mm. Hg.
Medium arteries (radial)	+110 mm. Hg.
Capillaries, between	+ 15 and + 20 mm. Hg.
Small veins	+ 10 mm. Hg.
Large veins in the neck, between	+ 5 and − 8 mm. of Hg.
Portal vein	+ 10 mm. Hg.
Inferior vena cava	+ 3 mm. of Hg.

The blood pressure in the pulmonary circulation is about one-sixth of that in the systemic vessels.

The arterial blood pressure may be *increased* by—

1. Increase of the force and rate of heart beat.

2. Constriction of the peripheral arterioles; cold therefore raises the arterial blood pressure.

3. Increase in the volume of fluid circulating, as after a good meal.

The arterial blood pressure may be *decreased* by—

1. Decrease in the force and rate of heart beat.

2. Dilatation of the arterioles.

3. Decrease in the volume of fluid circulating, such as occurs after bleeding.

The arterial blood pressure slightly rises in the morning and falls at night. Rest tends to lower the pressure, while exercise at first slightly increases it, though ultimately it lowers it.

The influence of gravity upon the circulation (hæmostatic pressure) is that the blood tends to accumulate in the veins of the lowest part. This is to a considerable extent overcome by two factors:—

1. Vaso-motor nerves causing vaso-constriction of the arterioles of the splanchnic area. When the erect posture is assumed, the fall of blood pressure in the medulla stimulates the vaso-motor centre whereby vaso-constriction in the splanchnic area occurs.

2. The "respiratory pump." During inspiration venous blood is induced to flow towards the thorax because of the increased negative pressure (−30 mm. Hg) which is there produced.

The influence of the splanchnic area upon the general blood pressure may be demonstrated as follows:—

A tame rabbit, with a pendulous abdomen, is held up by its ears; after a few struggles it becomes quiet, then unconscious, and in half an hour may die. Blood accumulates in the legs and pendulous abdomen (there being a want of vascular tone in "hutch" rabbits), and the brain becomes anæmic. The animal will recover consciousness if its abdomen is bandaged, or if it is placed in a horizontal position. Invalids frequently become giddy and faint on first rising from the horizontal position; this is due to want of tone in the vessels of the splanchnic area. The condition may be overcome by lying down and taking deep breaths.

CAPILLARY BLOOD PRESSURE.

This is estimated by observing the amount of pressure which is required to blanch a small area of skin. The capillary pressure is surprisingly high, so high that the thin capillary wall would be unable to withstand such a pressure were it not for the tension of the extravascular tissues. The capillary pressure depends upon the condition of the arterioles. If the arterioles to a part dilate, the capillary pressure rises; if they constrict, the capillary pressure falls. If, however, the venous pressure is raised, the capillary pressure must consequently rise too. Gravity very materially influences the capillary pressure. It is found that the capillary pressure in a finger is twice as high when the hand is hanging down as when the hand is raised to the top of the head.

VENOUS BLOOD PRESSURE.

The venous blood pressure, as a rule, is so low that a saline solution is generally used instead of Hg in the manometer.

The venous blood pressure is influenced by—

1. The presence of valves which prevent a backward flow; and,
2. Respiratory movements.

The general effect of inspiration is to draw venous blood into the thorax, thus emptying the large veins, with a consequent fall of venous blood pressure. The general effect of expiration is to cause a slight resistance to the flow of blood into the thorax, and consequently to raise the blood pressure in the large veins.

A venous blood pressure tracing taken in the neck shows larger waves due to respiratory movements, and smaller waves due to individual heart beats.

THE VASO-MOTOR MECHANISM.

It has been already stated that one of the most important factors in regulating the arterial blood pressure is the work of the muscular arterioles, and these vessels are under the control of the central nervous system.

The Vaso-motor Centre.—This is placed in the floor of the fourth ventricle, and commences about 3 mm. above the calamus scriptorius; it is ill defined, and it is possible that the nerve cells constituting the centre are scattered over a relatively large area. The centre is symmetrically placed on either side of the median line. In all probability it consists of two portions, namely, vaso-constrictor and vaso-dilator.

The vaso-motor centre has been located in the region indicated in the following manner. If a section is made between the medulla and the spinal cord in an animal, the arterial blood pressure rapidly falls because the centre is cut away from the spinal cord. If, on the other hand, sections are made through the higher portion of the medulla, there is no alteration of the blood pressure until the vaso-motor centre is encroached upon; and, as sections are made farther back, so the arterial blood pressure begins to fall; when the last section is made, which completely cuts off the vaso-motor centre from the cord, the blood pressure falls to zero. There are *subsidiary vaso-motor centres* in the grey matter of the dorsal region of the spinal cord. These are extremely active in the lower types, like the frog, but probably are not so active in the higher types, as man. These subsidiary centres of the cord of the frog may be demonstrated as follows. If the vessels in the frog's web are observed under the microscope, and the brain then destroyed, it will be seen that the vessels become dilated. This is due to the fact that the vaso-motor centre in the medulla is destroyed. The vessels, however, soon regain their tone, because the subsidiary centres in the cord take over the function of the higher centre. If the spinal cord is completely destroyed, the peripheral blood vessels dilate and do not recover their tone. Subsidiary centres may be demonstrated in the cord of the dog as follows. If the spinal cord of the dog is severed between the fifth and sixth cervical nerves, and the dog recovers the shock of the operation, the animal is said to have been rendered "spinal," its blood vessels recover their tonus, and the circulation goes on as if nothing had happened. This shows that there are centres in the spinal cord which are capable of performing the function of the highest centre. The vaso-motor centre is, to a very considerable extent, an *automatic* centre dependent upon a supply of oxygenated blood for its proper working. If the oxygen tension in the blood becomes low and the tension of the CO_2 rises, the centre for the time being becomes more active and the arterial blood pressure rises slowly. This condition is found in the early stages of asphyxia, but as the CO_2 contained in the blood increases, the centre becomes poisoned and begins to give out, and the arterial blood pressure gradually falls. When cerebral anæmia occurs the vaso-motor centre participates in the condition; the anæmia, however, increases the activity of the vaso-constrictor portion of the centre; the result is that the vessels in the splanchnic area constrict, causing a rise of active blood pressure and an increased blood supply to the brain, and in this way the central anæmia is overcome. The vaso-constrictor centre, however, is a *tonically acting* one, which means that it is persistently giving out impulses to the peripheral arterioles in order that they may be kept in a state of tonus. The centre, however, is capable of exhibiting rhythmicality, and its rhythmic action is shown in the Traube-Hering curves which are seen on the down-stroke of the blood-pressure tracing taken of an animal during the later stages of asphyxia. These curves also appear on the blood-pressure tracings of animals under the influence of an anæsthetic. They are produced by the vaso-constrictor centre sending out stronger, then weaker, impulses.

The vaso-constrictor centre is certainly a *reflex* one,
4· capable of being influenced by afferent impulses from without.
5· There is no doubt that certain drugs have a direct influence upon the vaso-motor centre, increasing its activity; such drugs include digitalis and strophanthus.

Afferent Impulses.—There are two kinds of these impulses which influence the vaso-constrictor part of the vaso-motor centre.

1. *Depressor Influences.*—These impulses normally start in

the heart, or at the commencement of the aorta, and the adequate stimulus for them seems to be a rise of endocardial or aortic pressure. They travel up the depressor nerve, when it exists as a separate nerve (rabbit, cat, horse), or through the depressor fibres in the vagus nerve to the vaso-motor centre, and their influence is to inhibit the activity of the vaso-constrictor part of the vaso-motor centre, and possibly also to increase the activity of a vaso-dilator centre; the result of which is that weaker vaso-constrictor impulses descend the spinal cord, the peripheral arterioles in the splanchnic area dilate, and the arterial blood pressure gradually falls.

Shock. — The condition known as shock (vaso-motor paralysis) is brought about by certain abnormal stimuli, such as are produced by a large cutaneous burn, especially if on the trunk, injury to a large nerve trunk, such as the sciatic or the cords of the brachial plexus, or injury to the spinal cord itself. These abnormal stimuli travel up the spinal cord to the vaso-constrictor part of the vaso-motor centre and inhibit its activity; the result is that the peripheral arterioles in the splanchnic area dilate, and the blood pressure gradually falls. Injury to the cord itself may cut off all efferent vaso-constrictor impulses. As a result of vaso-dilatation in the splanchnic area the brain is rendered somewhat bloodless (anæmic), and the patient may pass into a subconscious condition. If, however, the vital centres in the floor of the fourth ventricle—that is, the respiratory and the cardiac centres—are rendered anæmic, their activity may give out and the patient die. It is seen that shock is brought about either by abnormal afferent depressor impulses, or by cutting off efferent vaso-constrictor impulses which travel down the spinal cord. Shock may be appropriately treated by the application of a broad abdominal binder to prevent the accumulation of blood in the splanchnic pool, and by the administration of adrenalin or ergot, which act peripherally and tone up the arterioles; while barium salts—3 grs. of the chloride—which act directly on the muscle fibre, and not on nerve endings, are appropriate (Langdon Brown).

2. *Pressor Influences.*—If the upper cut end of a large nerve trunk, such as the sciatic, the cords of the brachial plexus, or the vagus nerve itself, is stimulated, afferent impulses travel up the spinal cord to the vaso-motor centre, which increase the activity of the vaso-constrictor part of the centre; stronger

impulses now travel down the spinal cord to the blood vessels in the splanchnic area, vaso-constriction takes place, and the arterial blood pressure is raised. The result of the application of a blister is very much of this nature. If a large blister or mustard plaster is applied to a large cutaneous area, the local result is vaso-dilatation of the cutaneous arterioles beneath the blister or plaster; but the general result is vaso-constriction and a slight rise of arterial blood pressure, brought about by afferent impulses which start in the irritated cutaneous area and travel up to the vaso-motor centre.

Efferent Impulses.—The vaso-constrictor impulses which start in the vaso-constrictor part of the vaso-motor centre travel down the spinal cord, probably in the mixed lateral tract on the same side as they arise in the medulla; there is no evidence of any crossing of the fibres. The nerve fibres, which bring down these impulses, traverse the cervical region of the cord, and travel into the grey matter of the dorsal region, where they arborise around the nerve cells found in the lateral cornu of the grey matter of the spinal cord. It should be noted that these lateral cornual cells exist only in the dorsal region of the cord. New fibres arise from these lateral corneal cells, and they travel straight through the anterior cornua of the cord (*vide* Fig. 86). These vasomotor fibres, which become finely medullated in the anterior root zone, leave the cord in the anterior nerve roots in the dorsal region. They then leave the anterior nerve roots, and travel to the nearest sympathetic ganglia. The fibres which go to the ganglia are known as the pre-ganglionic fibres (white rami communicantes). In the ganglia these finely medullated fibres lose their medullary sheath and arborise around the ganglion cells. These proximal sympathetic ganglia are cell stations for the vaso-constrictor fibres. New nerve fibres arise in these ganglion cells and leave the ganglia as non-medullated nerve fibres, they are called the post-ganglionic fibres (grey rami communicantes). As such they pass back to the nearest spinal nerve. The vaso-constrictor impulses for the body leave the spinal cord by the anterior roots of the spinal nerves from the second dorsal to the second lumbar inclusive. The vaso-constrictor impulses for the vessels of the head travel up through the first dorsal ganglion (ganglion stellatum), through the annulus of Vieussens to the inferior, middle, and superior cervical ganglia; *i.e.* ascend the sympathetic nerve chain in the neck. The cell station is in the superior cervical ganglion. The vaso-constrictor fibres for the arm have their cell station in the ganglion stellatum, and travel down by the motor nerves of the limb. The vaso-constrictor fibres for the leg have their cell station in the lower lumbar and sacral ganglia, and travel down the nerves to the lower extremity.

The vaso-constrictor fibres for the thorax and abdomen have their cell stations in the collateral ganglia, and these fibres pass along the sympathetic and splanchnic plexuses to the vessels of the thorax and abdomen respectively.

If pre-ganglionic nerve fibres are stimulated, vaso-constriction takes place. If the sympathetic ganglion is painted with a weak solution of nicotine, which poisons synapses and nerve cells, and then the pre-ganglionic fibre is stimulated, no vaso-constriction occurs; but if the post-ganglionic fibres are stimulated, vaso-constriction will take place beyond (Langley's nicotine experiment). If the cervical sympathetic nerve of a rabbit is divided, it is found, *inter alia*, that the blood vessels in the ear of the rabbit become dilated, and capillaries which were not obvious before the section come into view. If the upper or oral cut end of the sympathetic nerve is then stimulated with rapidly interrupted induction shocks, the arterioles of the ear of the animal become constricted, many of the small capillaries disappear from view, and the ear becomes pale (Claude Bernard's experiment). If the cervical sympathetic of the rabbit is divided, the blood vessels of the ear become dilated, but after a time they recover their tone; this is due to the nerve cells in the superior cervical ganglion exercising a *local vaso-motor control*; if, however, the superior cervical ganglion is excised, the arterioles of the ear remain permanently dilated.

That vaso-constrictor impulses travel down the nerves which are distributed to a limb may be demonstrated as follows:—

If the sciatic of a cat is exposed and cut, and the limb placed in a plethysmograph, and the peripheral cut end of the nerve stimulated by rapidly interrupted induction shocks, the muscles will not only be thrown into tetanus, but the limb will become smaller and paler, because of vaso-constriction brought about by the stimulation of the vaso-constrictor nerves. That vaso-constrictor impulses travel in the splanchnic nerves to the viscera may be shown by the following experiment. If the spleen, or the kidney, or part of the small intestine is placed in an air plethysmograph which is covered in by a plate of glass, and the nerves to the part are cut, it will be noted that the organ increases in volume and becomes redder. If the peripheral cut end of the nerves is then stimulated by rapidly interrupted induction shocks, the organ gets smaller and paler; this is due to vaso-constriction of the arterioles in the organ. It is believed that the vaso-constrictor fibres break up around the plain muscle in the middle coat of the arterioles, and these terminations may be influenced by certain substances which may be introduced into the circulation. If suprarenal extract is injected into the jugular vein of an animal, it stimulates the terminations of the vaso-constrictor fibres, causing a gradual rise of arterial blood pressure, and organs, such as the kidney, spleen, and intestines, diminish in volume. Extract of the nervous part of the pituitary body causes vaso-constriction in the splanchnic area, with the exception of the arterioles of the kidney, which appear to dilate under its influence. If a solution of choline or commercial peptone (albumose) is injected into the blood stream of an animal, it is found that the peripheral arterioles dilate and that the blood pressure gradually falls.

Raynaud's disease is due to a localised constriction of the arterioles in a part, so that the blood supply to the capillaries is practically cut off. The result of this is that a local syncope occurs, followed by a local asphyxia; if this condition is not relieved local gangrene or death may follow.

Erythromelalgia, on the other hand, is due to a permanent local dilatation of arterioles leading to capillary congestion; hence the redness of the part.

Vaso-dilator Impulses.—These impulses probably arise in the vaso-dilator portion of the vaso-motor centre, and travel down the spinal cord in the mixed lateral tract, traversing the grey matter and leaving the spinal cord by the anterior nerve roots in a similar way to the vaso-constrictor fibres. The vaso-dilator fibres are medullated, and, as medullated nerve fibres, they traverse the proximal sympathetic nerve ganglia, and travel as finely medullated nerve fibres to the peripheral ganglia, where they form cell stations and lose their medullary sheath. As examples of such peripheral ganglia may be mentioned the sub-maxillary ganglion, which is the cell station for the sublingual gland, and Langley's ganglion, which is the cell station of the sub-maxillary gland. There are other peripheral ganglia in the splanchnic area and along peripheral blood vessels.

Bayliss has found vaso-dilator fibres in the posterior nerve roots, so that it is possible that the posterior nerve roots contain efferent as well as afferent fibres. The facts obtained from experiments upon nerve degeneration, however, seem to show that there are no efferent fibres present. At the same time, it is possible that some of the nerve fibres in the posterior nerve roots may convey impulses both ways. Bayliss calls these efferent impulses along the posterior nerve roots *antidromic*, which indicates that they travel in the opposite direction to that usually traversed by posterior nerve root impulses.

If the chorda tympani nerve is cut and the peripheral cut end stimulated, the blood vessels to the sub-maxillary and sub-lingual glands become dilated, and there is also an increased flow of watery saliva. If the small petrosal nerve is cut and the peripheral cut end stimulated, the blood vessels in the parotid gland dilate. If the lingual nerve is cut and the peripheral cut end stimulated, the blood vessels in the side of the tongue dilate. If in a dog the nervi erigentes are cut and the peripheral cut end stimulated, the helicine arteries uncoil, and the cavernous tissue in the corpora cavernosa becomes flushed with blood and erection takes place. If, on the other hand, the sciatic nerve of an animal is cut and the peripheral cut end is stimulated by slowly interrupted induction shocks, say at intervals of about one second, vaso-dilatation occurs, showing that mixed nerves contain finely medullated vaso-dilator fibres. It is found that, after a mixed nerve has been sectioned and nerve degeneration allowed to take place, the vaso-constrictor fibres, which are non-medullated, degenerate before vaso-dilator fibres which are finely medullated, and these latter will respond to electrical stimuli.

Exposure to cold depresses the excitability of vaso-constrictor sooner than that of vaso-dilator nerves. If, therefore, the sciatic nerve of a cat is divided and the leg placed in ice-cold water, stimulation of the peripheral cut end of the nerve is followed by vaso-dilatation.

There is no evidence of vaso-motor nerves controlling the blood vessels of the pia-mater which supply the brain, the pulmonary arteries, and the coronary arteries. There are vaso-motor nerves supplying the portal vein, and in this way the main blood supply to the liver is regulated. The splanchnic area, so well supplied by vaso-motor nerves, has been described as the "resistance-box" of the circulation (Hill), by means of which variations in the systemic blood pressure are regulated; that is, there is a reciprocal action between the splanchnic area and the more peripheral portions of the circulation. Heat is associated with vaso-dilatation of the cutaneous arterioles, but in these circumstances there is vaso-constriction in the splanchnic area. During active digestion the splanchnic vessels are dilated; this is compensated for by vaso-constriction of the cutaneous arterioles. It has been stated that the arterioles of the brain have no vaso-motor nerves, so that to a certain extent the arterial supply to the brain is regulated by the peripheral (especially the splanchnic) arterioles. General vaso-constriction results in an increased supply of arterial blood to the brain, and, as the brain is contained in the skull, this increased arterial supply must be associated with a squeezing out of a certain amount of cerebrospinal fluid.

The Blood Flow in the Capillaries.—There is a constant slow stream of blood through the capillaries. Along the walls there is a slow stream of blood plasma containing a few colourless corpuscles; the central stream is much quicker, and contains the coloured corpuscles. In the smallest capillaries the coloured corpuscles roll along in single file, and may be seen to become temporarily altered in shape as they are squeezed around corners. Occasionally colourless corpuscles may be seen squeezing their way by amœboid movements between the endothelial cells lining the capillaries; they then invade the perivascular tissue; this is normal diapedesis.

THE VENOUS FLOW.

The onward flow of blood in the veins is due to—

1. The *vis a tergo*, which is the force due to the blood pressure started in the heart, and transmitted through the arteries, then through the capillaries to the veins.

2. The contraction of the muscles of the body around the thin-walled veins which press the blood on, its return being prevented by the valves which are present where gravity exerts

its influence. If the muscle of the vein walls is not fully developed it is liable to stretch, and the valves become incompetent. The result of this is that the veins are over filled, their walls become thinned, and the veins themselves tortuous (varicose veins).

The "tone" of the skin and tissues generally aids the venous flow.

3. The *vis a fronte* of the "thoracic pump"; this is due to (1) the suction action of the heart, mainly the ventricles, which, during their diastole, draw blood from the veins to the auricles and so become filled; and to (2) the aspiratory action of the thorax. During inspiration the negative pressure in the thorax becomes more negative; venous blood is consequently drawn into the thorax from the large veins.

A venous pulse may be obtained over the large veins at the root of the neck. The first rise is due to the distending right auricle, and the second to the active contraction of the auricle, and to a *slight* regurgitation of blood into the large veins from the right auricle (*vide* footnote, p. 203).

THE VELOCITY OF THE BLOOD-FLOW.

It is found that the velocity of the blood current is inversely proportional to the sectional area of the bed through which it flows.

In the aorta the rate is about 1 foot per second.

In the capillaries the rate is about 1 inch per minute.

In the veins, the capacity of which is twice or thrice that of the arteries, the velocity of flow is from a half to one-third of that in the corresponding arteries.

On approaching the heart the total sectional area of the veins becomes less and less, the velocity of the blood flow is therefore increased.

The velocity of the blood flow in animals may be ascertained by direct measurement by using appropriate instruments, thus:—

Volkmann's Hæmodromometer.—This consists of a long glass U-shaped tube filled with salt solution. The ends of the cut vessel are fixed to the two ends of the U-shaped tube. At a given instant blood is allowed to flow through the tube, and the time the blood takes to traverse the tube carefully noted. The sectional area of the tube should be the same as that of the blood vessel used in the experiment.

Ludwig's Stromuhr.—This consists of a glass tube with two bulbs, one on each limb (*vide* Fig. 28). The proximal bulb is filled with oil, and the distal one with defibrinated blood. The two limbs are connected with the cut ends of a blood vessel. When the bulbs are brought into proper position, and the blood allowed to flow from the proximal end of the artery into the bulb which contains the oil, the blood displaces the oil, the oil displaces the defibrinated blood in the distal limb, and the defibrinated blood enters the distal end of the cut vessel. Just as the oil, now in the distal limb, is about to enter the distal portion of the cut vessel, the bulbs are suddenly rotated so that the oil bulb is once more returned to the proximal end of the cut vessel.

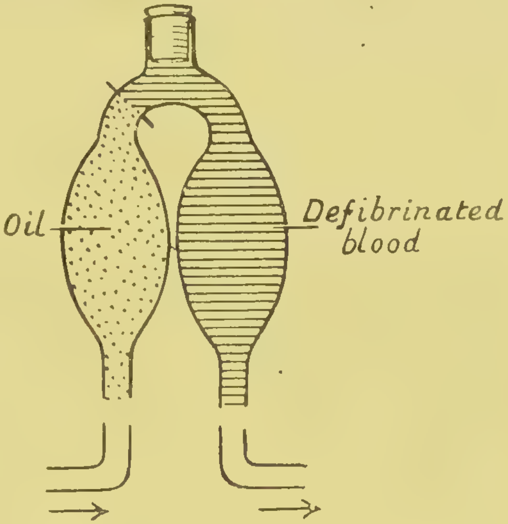

FIG. 28.—Diagram of Ludwig's stromuhr.

The velocity of the blood flow may be calculated from the formula $V = \frac{Q \cdot t}{T \cdot \pi r^2}$.

V = velocity of blood flow.
Q = capacity of one bulb.
t = number of times the bulbs have been rotated in a given time, T.
$\pi = \frac{22}{7}$.
r = radius of the blood vessel.

Tigerstedt's stromuhr works on much the same principle as Ludwig's,—one glass cylinder containing a metal ball replacing the two bulbs of Ludwig's stromuhr.

The Shortest Time of a Complete Circulation.—This has been obtained by injecting a solution of potassium ferrocyanide into the central cut end of the jugular vein of an animal, and by collecting blood from the opposite end of the vessel, the exact time being noted when this blood gives the prussian blue reaction. The disadvantage of the method is that bleeding takes place, which weakens the heart and slows the circulation. Investigations have been made on the horse, dog, and cat, and the conclusion come to is that the shortest time of a complete circulation corresponds with 27 heart beats.

THE ARTERIAL PULSE.

The pulse is a wave of pressure, and therefore of apparent expansion, which originates at the base of the aorta, and is due to the increase of lateral pressure caused by the entrance of the contents of the left ventricle into the already full aorta brought about by the contraction of the heart; the result of this is a charge in shape of the artery. The following diagram (after Robert Hutchison) shows the change in shape of an artery from an oval to a circular form during the passage of the pulse wave.

FIG. 29.

At the same time, there is a certain amount of straightening out of the artery, and not a real increase in the circumference of the vessel.

The strength of the pulse wave diminishes as the small arteries are reached. Its rate varies from 5 to 10 metres per second.

The pulse wave is most conveniently obtained over the radial artery, where it lies against the lower end of the radius.

On feeling the pulse the following points should be noted:—

1. The *frequency* of the pulse; the number of pulse waves per minute indicate the number of heart beats per minute, provided the heart beats are sufficiently strong to manifest themselves in the artery. The usual frequency is seventy-two beats per minute.

2. The *force* of the pulse; whether strong or weak: this indicates the force of the contraction of the left ventricle.

3. The *regularity* of the pulse. It should be quite re-

gular in time. An irregular pulse wave indicates irregular cardiac rhythm.

4. The *equality* of the pulse. The beats should be of equal force. If the waves are unequal it usually indicates that the heart beats are of unequal force too.

5. The *tension* of the pulse; this is indicated by the amount of force required by the palpating finger to obliterate the pulse wave.

6. The condition of the arterial wall; whether it is soft and elastic, or hard and calcareous, or definitely tortuous.

SPHYGMOGRAPHY.

The following figure represents a single pulse tracing (sphygmogram) of the radial artery taken with the Dudgeon sphygmograph.

On reference to the figure it will be seen that the portion of the tracing A C represents a shorter period of time than C G. This indicates that the time taken in the *apparent* expansion of the artery is shorter than the time during which the artery returns to its previous condition; in other words, the time of apparent expansion is less than the time of elastic recoil.

This time difference will be readily understood when it is remembered that the left ventricle drives the blood it contains into the aorta with suddenness and force, causing a sharp rise in arterial pressure and initiating the pulse wave. The recoil of the arteries is due to their own elasticity.

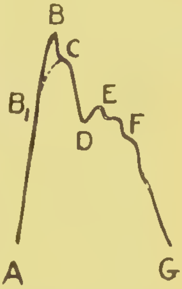

FIG. 30. Diagram of a single pulse tracing.

A B is the primary or percussion wave brought about by the sudden expansion of the elastic aorta, and this wave of altered pressure is transmitted throughout the arterial tree and is conveniently registered in the radial artery. The expansion of the aorta is due to the extra amount of blood which it receives during ventricular systole. The ascending part of the pulse wave is called the anacrotic limb, and the descending part of the wave the katacrotic limb.

The Katacrotic Limb.—On this limb may be seen the katacrotic waves, the first of which is shown at C. This is called the predicrotic notch. There are two chief explanations of the causation of the predicrotic wave.

1. That it is due to an elastic vibration of the arterial wall.
2. That it is due to the inertia of the lever of the sphygmograph.

If this latter view is correct the primary wave would be more correctly represented by the line A B_1 C.

The second katacrotic wave is the dicrotic wave D E, and the depression before it the dicrotic notch C D E. During the very earliest stage of cardiac diastole there is a suction action exerted by the left ventricle, which tends to draw blood from the aorta back into the cavity of the ventricle. This causes the aortic semilunar valves to fill, and consequently to close gently, then the elastic recoil of the aorta drives blood against the closed semilunar valves, so that at D another positive wave D E is originated at the valves, and propagated along the aorta and arterial walls generally towards the periphery. In other words, the positive onward wave D E is due to the blood being driven against the closed aortic semilunar valves. The nearer to the heart the sphygmographic tracing is taken, the more obvious is the dicrotic notch and wave. the distance p

Sometimes it is found that the dicrotic wave is much larger and more definite than is indicated in the accompanying diagram; this is due to the arteries being extremely elastic, and also the arterial blood pressure being somewhat low. In these circumstances the dicrotic wave may be readily palpated by the examining index finger; this is called the *dicrotic pulse*.

The third set of waves on the katacrotic limb consists of the post-dicrotic waves indicated by F. (Fig. 30). These are, in all probability, waves of oscillation, and are due to the elasticity of the walls of the aorta.

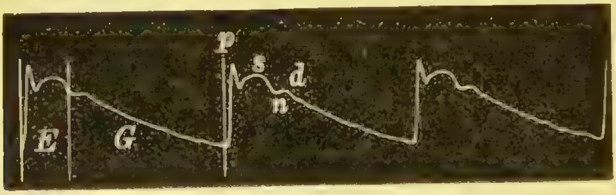

FIG. 31.—Sphygmogram of the radial pulse.
(*After* James Mackenzie.)

The space *E* represents the period of ventricular systole when the aortic valves are open; the space *G* represents the period of ventricular diastole; *s* is the wave due to the ventricular systole; *n* is the aortic notch; *d* is the dicrotic wave; *p* is the wave due to the inertia of the lever of the sphygmograph.

The Anacrotic Limb.—As a rule no secondary waves appear upon the primary or percussion wave of the pulse. If, however, the peripheral arterioles are constricted or definitely thickened, as they become in cases of chronic Bright's disease, the peripheral resistance is high; in these circumstances a secondary wave may appear on the anacrotic limb. This is the anacrotic wave, and the pulse is called the *anacrotic pulse.*

In the normal individual an anacrotic pulse may be obtained, according to von Kries, by raising the arm (Howell).

CHAPTER XVIII.

THE BLOOD.

THE FUNCTIONS OF THE BLOOD.

Blood conveys to the tissues proteins (probably also amino-acids), fats, carbohydrates, salts, water, and oxygen. It also supplies to the tissues the internal secretions which have been collected from organs of the body, such as the thyroid gland, pituitary body, and suprarenal capsule. It also contains various enzymes produced by cells in the body. Blood receives back from the tissues the products of katabolism, such as carbon-dioxide, uric acid, and urea. It is also a medium by which the body is defended against micro-organisms and toxins. By virtue of the living cells, which the blood contains, it may be regarded as a tissue, but one which is not under the control of the nervous system. As a rule, between the blood and the tissues is the intermediate *tissue fluid*, so that the changes which take place between the blood and the tissues occur through the tissue fluid. In certain organs of the body, however, the blood comes directly into contact with the tissues. This intimate relationship takes place in the red marrow of bone, in the spleen, in the hæmolymph glands, in the liver, and in the placenta. It is probable that the blood is never the seat of disease, but that the abnormal conditions which occur in it are the result of disease elsewhere, *e.g.* in the red bone marrow, spleen, and lymphatic glands. The amount of blood in the body of man is roughly one-twentieth of the body weight, the average volume being about $3\frac{1}{2}$ litres. This is distributed as follows :—

Heart, blood vessels, and lungs	$\frac{1}{4}$
Skeletal muscles	$\frac{1}{4}$
Liver	$\frac{1}{4}$
Skin and other tissues	$\frac{1}{4}$

THE PHYSICAL PROPERTIES OF BLOOD.

The red colour of blood varies. The blood is bright red in the arteries and deeper red in the veins. Blood is opaque because it contains solid elements; it is rich in salts, and therefore has a salty taste. The specific gravity varies between 1045 and ·1065; the average being about 1055, this specific gravity is readily obtained by the following method. A drop of blood is allowed to fall into fluids consisting of a mixture of glycerin and water; if the drop neither rises nor sinks the fluid has the same specific gravity as the blood. If the drop sinks, the specific gravity of the mixture must be raised; if the drop floats, the specific gravity of the fluid must be lowered. A mixture of chloroform and benzene has also been used in order to obtain the specific gravity of the blood.

The reaction of blood is alkaline, due to alkaline sodium phosphate. This alkalinity, however, varies; it is more alkaline after a meal, and becomes less alkaline after exercise.

COMPOSITION OF THE BLOOD.

Blood consists of a fluid, the liquor sanguinis or plasma, which constitutes about three-fifths of the whole blood volume. Suspended in the liquor sanguinis are the solid elements, which constitute about two-fifths:

Blood
- $\frac{3}{5}$ Plasma
- $\frac{2}{5}$ Corpuscles
  - Coloured corpuscles.
  - Colourless corpuscles.
  - Blood platelets.

BLOOD PLASMA.

Blood plasma, or liquor sanguinis, constitutes the fluid part of the blood as it circulates in the blood vessels. It may be obtained by one of the following methods, which are employed in order to prevent the blood clotting.

1. By drawing blood from a freshly cut blood vessel into an equal volume of saturated solution of sodium sulphate and then rapidly stirring. The mixture is then left in a cool place for twenty-four hours. The blood corpuscles settle to the bottom of the vessel, and salted plasma separates out. This

plasma may be made to clot by diluting it with water and adding a little fibrin enzyme.

2. Blood is drawn from a cut blood vessel straight into a 0·4 per cent. solution of potassium oxalate dissolved in normal saline solution made with distilled water. The mixture is stirred during the addition of the blood, and the vessel is then put into a cool place for twenty-four hours. During this time the corpuscles settle, calcium oxalate is precipitated, and blood plasma separates out. This is sometimes known as oxalated plasma. This plasma may be made to clot by the addition of a small amount of a soluble calcium salt.

3. Blood may be drawn into a solution of potassium citrate, and after the two have been stirred and the solution kept in a cool place, citrated plasma separates out. The potassium citrate combines with the calcium salts in the blood to form calcium citrate, which though soluble does not ionise. The mixture of blood and potassium citrate may be readily dealt with by centrifugalisation, subsequently the red corpuscles are found in a mass at the bottom of the tube, the colourless corpuscles form a thin yellowish-white layer on the top of the red layer, and the citrated plasma appears as a clear solution uppermost.

4. Blood plasma may also be obtained by drawing blood into a solution of sodium fluoride; after the mixture has been allowed to stand in a cool place, blood plasma separates out. Sodium fluoride prevents the formation of the activator thrombokinase.

5. If a solution of commercial peptone, which consists chiefly of proteose, is injected into the veins of an animal and allowed to circulate for a short time, and blood is then drawn into a clean vessel and kept in a cool place, the blood will not clot. The corpuscles settle, and plasma may be pipetted off; this is sometimes called "peptone plasma." Peptone plasma may be made to clot by passing a stream of CO_2 through it. It is a remarkable fact that, if a solution of proteose is injected into the blood stream, the colourless corpuscles begin to disappear from the blood. This fact may be readily observed by making film preparations of the blood before and after the injection of the proteose. If blood is drawn *into* a solution of commercial peptone, clotting is delayed, but it eventually occurs.

6. A saline extract of the glands which pour their secretion into the buccal cavity of the leech is made, and this extract of

hirudin is injected into the venous blood stream of an animal and allowed to circulate. After a time some blood is collected in a vessel; it is found that, after being allowed to stand, the corpuscles settle, and blood plasma separates out on the top.

In the methods described above the blood corpuscles may be very readily separated from the plasma by the use of the centrifugal machine.

7. If the blood of a horse is drawn into a vessel surrounded by a freezing mixture, the corpuscles gradually settle and blood plasma separates out. This "cooled plasma" clots on being warmed. It is obvious that the blood must not be frozen.

8. If a few inches of the jugular vein of a horse are carefully excised with the contained blood, and this venous tube is hung up in a cool place, the blood corpuscles settle and blood plasma remains on top. This is the "living test tube" experiment.

The Characters of Blood Plasma.—Blood plasma, obtained in this way, is a straw-coloured alkaline fluid with a specific gravity of 1027.

Composition of Blood Plasma.—Blood plasma consists of water 90 per cent., and solids 10 per cent. The solids, which are chiefly in solution, consist of proteins, fat, carbohydrates, inorganic salts, and organic extractives. Blood plasma contains certain gases in solution—oxygen, carbon-dioxide, and nitrogen.

The Proteins of Blood Plasma.—Blood plasma contains 8·0 per cent. of protein, composed as follows: fibrinogen, 0·4 per cent.; serum globulin, 3·8 per cent.; serum albumin 4 per cent., and a trace of fibrinoglobulin.

FIBRINOGEN.—It should be noted what a small proportion of fibrinogen is present in blood plasma. This is the precursor of fibrin, which is the basis of blood clot. Fibrinogen may be precipitated from its solution by adding an equal volume of a saturated solution of sodium chloride (26 per cent.). This reduces the sodium chloride present to 13 per cent. Fibrinogen coagulates at 56° C., and is insoluble in distilled water. It is soluble in normal saline solution 0·9 per cent., and is precipitated by stronger salt solutions, such as saturation with sodium chloride, sodium sulphate, or magnesium sulphate.

SERUM GLOBULIN.—Serum globulin may be precipitated by complete saturation with magnesium sulphate or sodium sulphate crystals, and by half saturation with ammonium sulphate solution. It is coagulated at 75° C. It seems that serum globulin consists of two portions—euglobulin, which is precipitated by dialysis, and pseudo-globulin, which is not so precipitated. The three globulins of blood plasma may be separated from one another by ammonium sulphate. Fibrino-globulin is precipitated by 25 per cent. solution of ammonium sulphate; euglobulin is precipitated by 33 per cent. solution of ammonium sulphate; and pseudo-globulin is precipitated by 50 per cent. solution of ammonium sulphate. It is obvious, therefore, that half saturation with ammonium sulphate precipitates the three globulins present.

SERUM ALBUMIN.—Serum albumin is the most abundant protein of blood plasma. It is precipitated by complete saturation with ammonium sulphate crystals. It is said that human blood contains three varieties of serum albumin, which may be separated by fractional heat coagulation,—α-serum albumin, which is coagulated at 73° C.—this variety is absent from the blood of the horse, ox, and sheep; β-serum albumin, which coagulates between 77° and 79° C.; and γ-serum albumin, which coagulates between 84° and 86° C. These last two are absent from the blood of cold-blooded animals, such as the frog and the toad. Serum albumin is lævo-rotatory 56°, and is not precipitated by ether, even after the solution has been made just acid with sulphuric acid. In this it differs from egg albumin, which is lævo-rotatory 35°·5, and is precipitated by ether after a drop of sulphuric acid has been added to the solution.

The Fats of Blood Plasma.—If the blood plasma is obtained from an animal which has just had a fatty meal, such as milk, the blood plasma will have a milky appearance; this is due to the absorbed fat, such as triolein, tripalmitin, and tristearin. In ordinary circumstances fats soon disappear from the circulating plasma. Blood plasma contains two lipoids—cholesterin and lecithin.

The Carbohydrates of Blood Plasma.—Blood plasma, obtained from the blood of the portal vein, contains the glucoses—dextrose, lævulose, and galactose. Blood plasma, obtained from the blood of an artery, contains dextrose chiefly. The blood plasma of a lactating woman occasionally contains a little lactose.

Generally speaking, the amount of dextrose in blood plasma varies between 0·12 and 0·2 per cent. If the percentage rises beyond 0·2, the cells of Bowman's capsule of the kidney excrete it into the urine. Blood plasma contains no glycogen, and, even if glycogen is introduced into the vein of an animal, it rapidly disappears from the blood stream, being there converted by an enzyme into dextrose.

The Salts of Blood Plasma.—Blood plasma is rich in soda salts. It also contains potash salts. The more important salts present, however, are sodium chloride, sodium carbonate, alkaline sodium phosphate, some calcium phosphate, calcium chloride, and ammonium carbonate.

Free acids and acid salts entering the blood are neutralised, partly by the Na_2HPO_4, which is converted into NaH_2PO_4, and which is excreted in the urine; and partly by the Na_2CO_3 with the evolution of CO_2, which is excreted by the lungs. If more acid enters the plasma than can be dealt with in this way, the excess combines with the ammonium carbonate, and the salt so formed is excreted in the urine.

The molecular concentration of plasma is isotonic with a 0·9 per cent. solution of sodium chloride.

The Organic Extractives of Blood Plasma.—The chief of these is urea, the amount varying between 0·02 and 0·04 per cent.; this is mainly derived from the liver. There are also present traces of hypoxanthine, xanthine, and uric acid as a soluble urate, and creatinine, which is formed in the liver. Amino-acids are also present is a very small quantity.

The Gases of Blood Plasma.—If the blood plasma is subjected to the air pump, it is found that of the gas obtained there is carbon-dioxide 35 per cent., nitrogen 2·5 per cent., and oxygen 0·26 per cent.

The composition of plasma remains remarkably constant, and this is due to two factors—

1. The renal cells seem to regulate the composition of the plasma, and if the percentage of the various constituents rises the renal cells excrete the excess.

2. Excretion into, or absorption from, the tissue fluid spaces in the body.

THE COAGULATION OF BLOOD.

When blood leaves the blood vessels, and occasionally within the vessels, it clots. The use of this extravascular clotting is to prevent further hæmorrhage. The coagulation or clotting of blood may be divided into three stages—

1. The blood becomes viscous; this stage is delayed if the blood is kept cool.

2. Gelatinous, when the blood becomes solid.

3. The solid mass contracts, and squeezes out a straw-coloured fluid serum. After some hours the red clot shrinks and floats in the serum.

Composition of the Blood Clot.—The blood clot consists of fine filaments of fibrin which form a network. This fibrin entangles the red blood corpuscles, the white blood corpuscles, and the blood platelets. The amount of fibrin in the blood clot is very small, varying between 0·1 to 0·4 per cent. The blood clot therefore consists mainly of red blood corpuscles.

When blood leaves the blood vessels and comes in contact with the tissues, in normal circumstances, it clots or coagulates. Occasionally thrombosis, or blood clotting, occurs within the blood vessels. There are two important questions to settle—

1. Why does the blood clot when it leaves the blood vessels and comes into contact with the tissues? and,

2. In normal circumstances, why does blood not clot in the blood vessels?

Blood clots, when it leaves the blood vessels and gets in contact with the tissues, in order to prevent further hæmorrhage, and blood coagulation may be considered to be the earliest stage in the repair of the injury which caused the hæmorrhage. There are many factors concerned in blood clotting, some of which may be deduced by methods which are used in preventing the blood from clotting, and therefore in obtaining the blood plasma. Salted plasma is obtained by drawing fresh blood into an equal volume of a saturated solution of sodium sulphate or magnesium sulphate; after the blood corpuscles have settled the salted plasma remains on the top. It is supposed that this plasma remains unclotted because the salt used, partially, or possibly completely, precipitates the fibrinogen present; that is to say, fibrinogen in solution is essential for blood clotting, and when it no longer exerts its activity, because it is more or less thrown out of solution, the plasma does not clot.

At the same time, the blood corpuscles settle at the bottom of the vessel, and the white blood corpuscles and the blood platelets are no longer in intimate relationship with the salted plasma, and it is therefore surmised that the white blood corpuscles and the blood platelets are essential for the clotting of blood. It is believed that the blood platelets, and possibly the leucocytes, and, in some circumstances, the cells of the tissues, shed out a substance which is called thrombogen, or prothrombin, and it is this substance which is so essential for blood clotting. The thrombogen, or prothrombin, is of the nature of a nucleo-protein. It has been demonstrated that nucleo-protein, derived from other cells than those in the blood, is capable of bringing about blood clotting. A solution of nucleo-protein may be obtained by one of the following methods:

I. THE SODIUM CHLORIDE METHOD.—If an organ rich in cells, such as the kidney or the thymus gland of a rabbit, is finely divided, and ground up thoroughly in a mortar with an equal volume of sodium chloride crystals, and water is added, a sticky mass is produced. If this viscid material is poured into a long column of water, the mass first falls to the bottom of the water, but after a short time a light sticky material rises to the top. This sticky material is nucleo-protein. It may be readily collected and dissolved in a 1 per cent. solution of sodium carbonate. It should then be filtered, when a clear solution of nucleo-protein will be obtained.

II. WOOLDRIDGE'S METHOD.—An organ rich in cells is carefully minced as before, and extracted for twenty-four hours with a dilute solution of sodium chloride. The sodium chloride dissolves out the nucleo-protein, which may be precipitated by the addition of a little weak acetic acid or sulphuric acid, and the precipitate redissolved in a 1 per cent. solution of sodium carbonate.

If a strong solution of nucleo-protein is allowed to run quickly into the jugular vein of an anæsthetised rabbit, death occurs almost at once, and this is due to *intravascular* coagulation. If a post-mortem examination is made, organised blood clots may be removed from the superior and inferior vena cava and also from the portal vein; the blood clot, however, is most organised in the portal vein. This experiment shows that any nucleo-protein of sufficient strength aids in the coagulation of the blood, and it has already been stated that prothrombin, or thrombogen, is of the nature of nucleo-protein.

In the preparation of blood plasma it was seen that, if fresh blood is drawn into a 0·4 per cent. solution of potassium oxalate in salt solution, and the blood and oxalate solution thoroughly mixed, after the corpuscles have settled in the vessel, oxalated plasma remains. The effect of the potassium oxalate is to deprive the plasma of its soluble calcium salts, and so long as there are no soluble calcium salts in the plasma, the plasma will not clot. If a little oxalated plasma is put into a test tube, and a few drops of calcium chloride are added, and the mixture kept at body temperature, clotting takes place; that is, as soon as soluble calcium salts are returned to the plasma clotting takes place. From this it is concluded that calcium salts in solution are necessary for blood clotting. It will be remembered that, if blood is drawn into a solution of potassium citrate, calcium citrate is formed, and the blood does not clot, but that calcium citrate is not precipitated, it being a soluble salt, yet calcium citrate in solution does not take the place of calcium chloride. It is found, however, that calcium citrate does not ionise when in solution, whereas calcium chloride does. The conclusion drawn, therefore, is that there must be not only a soluble calcium salt present in the blood to aid the clotting, but that it must be a soluble calcium salt which readily ionises; in other words, there must be *free* calcium ions present.

If blood is drawn from a cut vessel in the neck of a pigeon *straight* into a clean test tube, it is found that that blood will remain unclotted for many hours. The blood of a pigeon contains very few blood platelets, and it will be noted that the blood has not been allowed to come in contact with the tissues in the neck. It is concluded that the tissues generally secrete an activating agent, which is called thrombokinase, and this activating agent may also be produced by the blood platelets and the white blood corpuscles in the blood itself.

It will be noted that another method of obtaining blood plasma is by drawing blood into a solution of sodium fluoride. Now, sodium fluoride does not combine with the calcium salts, yet sodium fluoride prevents the blood clotting. It is believed that the sodium fluoride poisons the blood platelets and the white blood corpuscles, and so prevents the liberation of the activating agent thrombokinase. From these experiments it is concluded that blood clotting depends upon the following conditions:—

1. The production of thrombogen, or prothrombin, which is derived chiefly from the blood platelets, partly from the leucocytes, and, in certain circumstances, from the tissue cells themselves.

2. The presence of free calcium ions.

3. The presence of an activating agent, thrombokinase, which is analogous to the enterokinase, the activating agent of the succus entericus, and this thrombokinase is produced mainly by the tissues over which the blood flows, but it *may* be derived from the blood platelets and the leucocytes.

The activator thrombokinase, in the presence of free calcium ions, activates the thrombogen, or prothrombin, with the result that the active thrombin, thrombase, or fibrin enzyme is formed. Fibrin enzyme so produced acts upon soluble fibrinogen, and converts it into insoluble fibrin. The fibrin is the basis of the blood clot.

If a small drop of blood is placed on a glass slide and allowed to clot, and a cover-glass is placed on it, and a solution of borax carmine washed through under the cover-glass, the borax carmine will cause the red blood corpuscles and many of the white blood corpuscles to be removed. The borax carmine will, however, stain the fibrin and small granular masses in connection with the fibrin filaments. If this preparation is examined under the high power of the microscope, it will be seen to consist of fine filaments of fibrin, many of which are connected with small irregular granular masses, which are probably either blood platelets or broken white blood corpuscles.

It will now be understood why it is that blood clots when it leaves the vessels and comes in contact with the perivascular tissues.

Turning to the second question, why is it that, in normal circumstances, the blood does not clot in the blood vessels. There is no doubt that one reason is that the blood circulates, that is, that it does not remain stationary. In abnormal circumstances, when the blood does clot in the vessels, the clots are found where the blood stream is slowest, such as in the veins, or where the blood stream is stopped altogether;

this occurs when an artery has been ligatured, but when the blood circulates freely, blood clotting does not, in normal circumstances, occur. It has been seen that circulating blood contains all the essentials for blood clotting; that is, thrombogen may be formed from the blood platelets and the leucocytes, that free calcium ions are present in the blood plasma, and thrombokinase may be formed from the blood platelets and the leucocytes. That is, there are present in the blood all the factors to produce fibrin enzyme, and fibrinogen normally exists in blood plasma. What, then, prevents the fibrin enzyme from acting upon the fibrinogen? It has been shown already that a strong solution of nucleo-protein causes intravascular coagulation, and that the most organised blood clot is found in the portal vein; that is, in the blood stream on its way to the liver. It is surmised that the liver cells produce an anti-body called anti-thrombin, which neutralises the fibrin enzyme, or thrombin, which exists normally in the blood stream.

It has been shown also that if albumose is injected into the jugular vein of an animal and allowed to circulate, when that blood is drawn, it does not clot. It is concluded that the albumose stimulates the liver cells to pour out a large amount of anti-thrombin which neutralises the thrombin present. Leech extract, or hirudin, also acts by neutralising the thrombin. Although a leech is capable of extracting only about 2 to 3 drms. of blood from a wound, the patient frequently loses more than that small amount of blood from the leech bite; this is due to the fact that the buccal glands of the leech secrete hirudin, which is probably the same thing as anti-thrombin; the blood is consequently prevented from clotting, and bleeding goes on. Hæmorrhage from a leech bite may be stopped by thoroughly washing the wound in order to remove the hirudin; or, if the leech bite is excised, the blood will immediately clot in the region of the wound.

If a weak solution of nucleo-protein is slowly injected into the blood stream of an animal, it is found that there is a diminished coagulability of the blood. This is called the *negative phase* of intravascular coagulation, and it is believed that this weak solution of nucleo-protein acts in very much the same way as albumose; that is, by causing the liver to secrete more anti-thrombin. Moreover, if this negative phase is first produced, and then a stronger solution of nucleo-protein is quickly injected, the usual *positive phase* of intravascular coagulation does not occur; that is, the first injection of the weak solution of nucleo-protein has caused the animal to become immune to a stronger solution, possibly by the production of a large amount of anti-thrombin. It may be concluded, then, that the blood in normal circumstances does not clot in the vessels—(1) Because it is kept moving; and (2) because the small amount of fibrin enzyme which normally exists in the blood plasma is neutralised by the anti-thrombin secreted by the liver cells.

Increased Coagulability.—In abnormal circumstances, however, the blood does clot within the living vessels—

1. If the endothelial lining of the blood vessels is injured. This may be brought about by the introduction of a needle, and by scratching the inner lining of the vessel.

2. In certain diseases, such as typhoid fever, when thrombosis frequently occurs in the veins of the body.

3. After child-birth thrombosis occasionally occurs in the veins of the leg. The exact physiological explanation of these thromboses is not clear, but it may be due to the formation of too much fibrin enzyme through the disintegration of the tissue cells; or it may be due to the production of too little anti-thrombin by the liver cells; or both factors may be at work in these pathological thromboses.

Decreased Coagulability.—In the disease called hæmophilia, in which there is a tendency to uncontrollable hæmorrhage, the coagulation time of the blood is much retarded. Wright has found the coagulation time to be as long as twenty-three and even forty-five minutes (Osler).

SCHMIDT'S METHOD OF OBTAINING FIBRIN ENZYME, OR THROMBIN.

Twenty volumes of absolute alcohol are added to 1 volume of blood serum; these are thoroughly mixed and allowed to stand in a cool place for from four to six weeks. All the protein present, including the fibrin enzyme, is precipitated; prolonged contact of precipitated protein with alcohol causes the coagulation of the protein. Fibrin enzyme, however, is not coagulated by contact with alcohol; the alcohol is then drawn off, and the coagulated protein washed with water, the uncoagulated but precipitated fibrin enzyme goes into solution. For practical purposes, however, a solution of fibrin enzyme may be obtained by diluting ordinary blood serum with tap water.

BLOOD SERUM.

Blood serum is the straw-coloured fluid which is squeezed out of a blood clot. Its specific gravity is 1027; its reaction is alkaline.

Composition.—Water, 90 per cent.; solids, 10 per cent. The solids are much the same as those of blood plasma, with the exception that there is no fibrinogen, it having gone to form fibrin. There is present an appreciable amount of fibrin enzyme. The proteins present are serum globulin, serum albumin, and fibrino-globulin. The light yellow colour of serum is due to a pigment, serum lutein. This pigment has a reddish tinge when a large volume of serum is examined. Care must be taken not to mistake it for hæmoglobin.

The Characters of Fibrin.—Fibrin is a coagulated protein, and may be obtained in the following manner:

If a large volume of freshly drawn blood is rapidly whipped with twigs, blood clotting takes place, fibrin is formed, and adheres to the twigs. From these it may be collected and washed in tap water. It is found to be a yellowish, elastic, insoluble stringy-like mass, consisting of pure protein. If placed in alcohol it shrinks, due to the abstraction of water.

THE COLOURLESS BLOOD CORPUSCLES.

In health the proportion of colourless corpuscles is 1 to about 500 coloured corpuscles, and the blood contains from 5000 to 10,000 leucocytes per cubic millimetre. After a meal the number of colourless corpuscles in the blood increases as much as 20 per cent. (digestive leucocytosis). The increase is chiefly in the polymorpho-nuclear leucocytes and the lymphocytes. During the early days of childhood, and of pregnancy too, there is a leucocytosis. When at rest the colourless corpuscles form nearly spheroidal masses of granular protoplasm. In all cases one or more nuclei exist in each corpuscle, and many of the cells exhibit amœboid movements. The average diameter of the colourless cells is $\frac{1}{2500}$ of an inch. Kanthack and Hardy have very materially enlarged our knowledge of the various types of colourless blood corpuscles. These may be described under the headings of leucocytes, lymphocytes, and hyaline cells. The following classification is a useful one:—

I. **The Polymorpho-nuclear Leucocytes.**—These cells contain several nuclei united together by very fine threads of chromatin. Their protoplasm is filled with fine granules which stain readily with acid dyes like eosin; hence they are known as the finely granular eosinophilous or oxyphilous cells. These were styled by Ehrlich neutrophils, as he thought that the granules were stained with neutral dyes only; but Kanthack and Hardy have proved that Ehrlich's neutral stain must be considered as a weak acid dye.

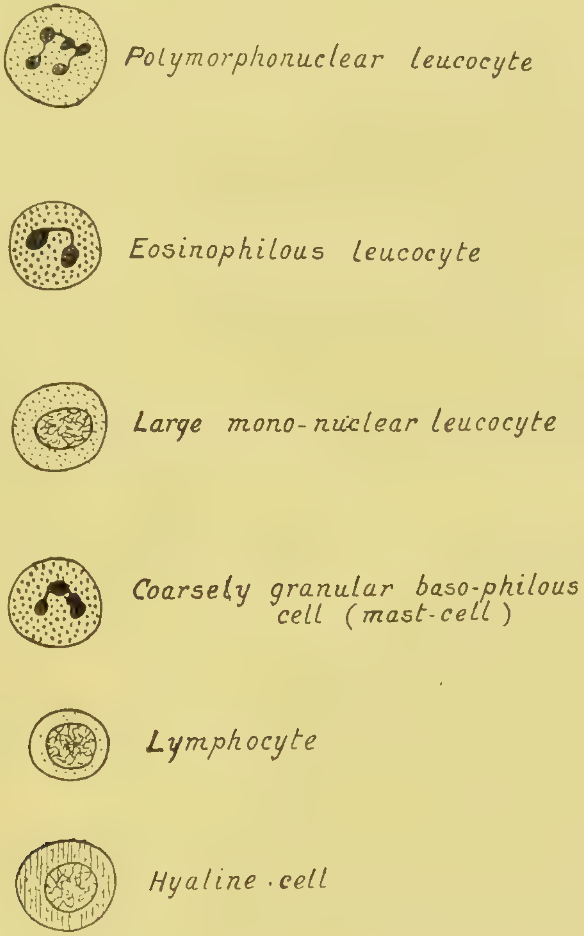
Polymorphonuclear leucocyte
Eosinophilous leucocyte
Large mono-nuclear leucocyte
Coarsely granular baso-philous cell (mast-cell)
Lymphocyte
Hyaline cell

FIG. 32.—The colourless blood corpuscles.

Polymorpho-nuclear cells are the most important of the leucocytes, constituting as they do about 70 per cent. of the total number of colourless blood corpuscles. Polymorpho-nuclear cells are most actively amœboid, and this gives them the power of ingesting foreign particles, such as carbon, and also the power of digesting bacteria, a process known as phagocytosis. Metchnikoff has applied the term microphage to this type of cell. In all cases of acute inflammation leading to suppuration and abscess formation, the polymorpho-nuclear leucocytes, passing from the capillary blood stream, predominate in the inflamed area. The polymorpho-nuclear leucocyte is the characteristic pus cell. It is actively phagocytic, particularly towards bacteria. It secretes substances of the nature of enzymes, and either while active or during its dissolution liberates anti-toxic and anti-bacterial substances; the latter are known as bacterio-lysins. In diabetes mellitus these cells contain an excess of glycogen.

II. **The Eosinophilous Leucocytes,** or the coarsely granular oxyphilous cells.

The nucleus is usually single and well defined, but it may be irregular; the granules in the protoplasm are large and coarse, and are deeply stained by acid aniline dyes, such as eosin; hence they are called acidophilous or eosinophilous cells. In the human blood they comprise only about 4 per cent. of the total leucocytes, although they are more numerous in the blood of the horse. These cells are not so actively amœboid as the polymorpho-nuclear cells, and are rarely phagocytic. These cells are formed partly in the red marrow of bone and partly in other connective tissues. The coarsely granular eosinophils are rarely found in the inflammatory process, though they are noticeably increased in number in certain diseases, such as trichinosis and intestinal parasites (helminthiasis), also in asthma.

III. **The Mononuclear Leucocytes.**—These cells have a single nucleus with fine granules in their protoplasm; these granules readily stain with basic dyes like methylene blue, hence they are spoken of as finely granular basophilous cells. There are from 1 to 2 per cent. of these cells present in the blood.

IV. **Coarsely Granular Basophilous Cells.**—These are large cells which are found in the connective tissue in the animal kingdom generally from the frog upwards, and are known as mastzellen (mast cells). Each cell has a central lobed nucleus, and the protoplasm contains coarse granules which readily stain with methylene-blue. These cells are particularly abundant in any area affected with sub-acute inflammation. Maximow states that in the course of the process of inflammation these cells disintegrate. They increase perceptibly in the blood of persons suffering from spleno-medullary leucocythæmia. Normally, however, there is only 0·5 per cent. of these cells in the blood.

V. **The Lymphocytes.**—These cells have a large spherical nucleus with a *small* amount of almost clear protoplasm around them; and are just a little larger than the coloured corpuscles. They constitute 20 per cent. of the total colourless corpuscles. Lymphocytes are formed in the lymphatic glands, Peyer's patches, solitary glands of the intestine, and the spleen. The lymphocytes are only slightly amœboid; they do not migrate very actively from the capillaries to the injured area in acute inflammations. In chronic inflammations, however, these cells preponderate, and constitute the chief element in the small round-celled exudation. The lymphocytes are not phagocytic for bacteria, but the lymphocyte does ingest particles of inert matter.

VI. **Hyaline Cells.**—These cells have a large spherical nucleus, and contain much more protoplasm than the lymphocytes. The protoplasm is finely granular, and stains slightly with methylene-blue; that is, the granules are very finely basophilous. These cells are phagocytic, and constitute about 3 per cent. of the colourless corpuscles. It is possible that they are derived from the endothelial lining of the blood vessels.

The nuclei of all these varieties of colourless blood corpuscles are basophilous, which means that they have a strong affinity for basic aniline dyes, such as methylene blue; but the nuclei may also be readily stained with hæmatoxylin. In passing it may be noted that by the process of inflammation is meant those changes which take place in the blood stream and the perivascular tissues when they react to an injury (*vide* p. 270).

Many of these characteristics of the colourless blood corpuscles may be produced by making film preparations of blood as follows:—A cover-glass must be previously thoroughly cleaned by placing it in strong nitric acid, and then transferring it to alcohol. It should then be dried between pieces of filter paper, and not touched by the fingers. A very thin blood film must be spread over the cover-glass and then allowed to dry. When dry, one drop of Jenner's stain [1] is placed on the film and left there for five minutes. The excess of stain is then washed off with distilled water, the film dried between pieces of filter paper, and further dried by holding near a flame; the cover-glass is then mounted film down in Canada balsam.

The total number of colourless corpuscles in human blood varies between 7000 and 10,000 per c.mm. Assuming the total number of colourless corpuscles in 1 c.mm. of blood to be 7500, the proportion of the various components is as follows (R. Hutchison):—

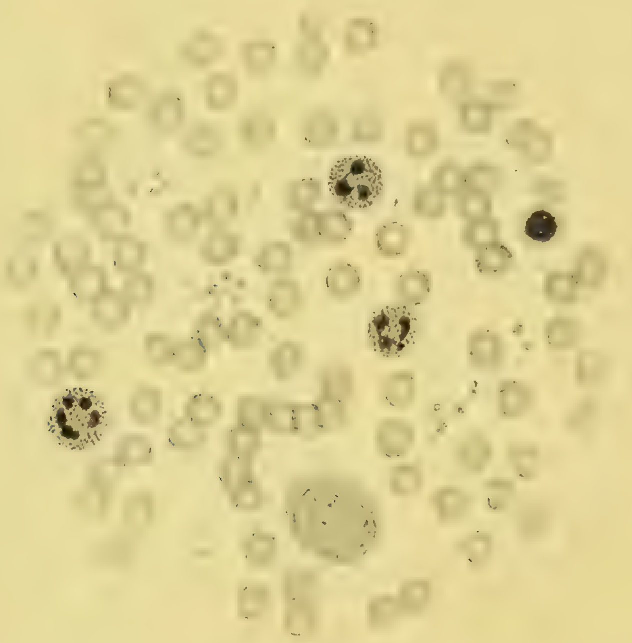

FIG. 33.—Diagram of a normal blood film. (Gibson and Russell.)

Polymorpho-nuclear cells	5000
Lymphocytes	2000
Large mononuclear cells	350
Eosinophils	150

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[1] Jenner's stain consists of a methyl-alcohol solution of the filtered residue, which is obtained by adding a 1·2 per cent. watery solution of eosine to 1 per cent. solution of methylene blue.

At birth the total number of leucocytes is 17,000 per c.mm., at the end of the first year the number is 14,000, and at the end of the third year the normal number is reached.

Enumeration of the Colourless Corpuscles by the Thoma-Zeiss Hæmacytometer.—1. The blood is drawn up into the graduated capillary pipette to the mark 1.

2. A coloured isotonic salt solution is then drawn up the pipette until the fluids in the tube fill the bulb, and stand at the level marked 2. (Toison's fluid is a useful one for the purpose; its composition is distilled water 160 c.c., glycerin 30 c.c., sodium sulphate 8 grms., sodium chloride 1 grm., methyl violet a trace. This stains the colourless corpuscles so that they may be more easily counted.)

3. The blood and the coloured fluid are well mixed by shaking the pipette. In the bulb there is a small glass bead which aids the mixing process. The mixture in the bulb consists of blood 1 part, coloured saline solution 9 parts.

4. The coloured fluid which is in the pipette as far as 1 is expelled; it contains no blood.

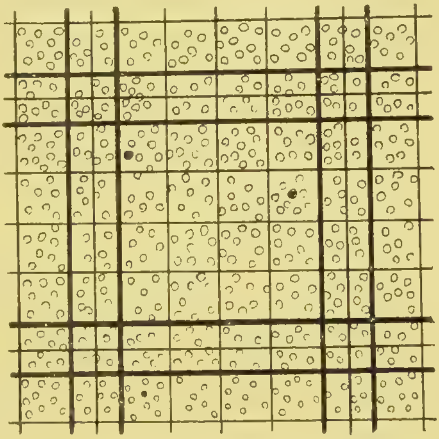

Fig. 34.—Blood corpuscles lying on the microscopic squares of a Thoma-Zeiss hæmacytometer. (*After* Gibson and Russell.)

5. A drop of the mixture is next expelled into the cell in the glass slide, the cell is filled and then covered with the thick cover-glass provided. At the bottom of the cell is ruled a square millimetre divided into 400 squares of one-twentieth of a millimetre each. The depth of the cell is one-tenth of a millimetre. The volume of the diluted blood opposite each ruled square, therefore, is $\frac{1}{20} \times \frac{1}{20} \times \frac{1}{10} = \frac{1}{4000}$ of a c.mm. The squares are further divided by double lines into groups of 16; this is to facilitate counting.

6. The corpuscles are allowed to sink, and the colourless corpuscles, now stained violet, are counted on one hundred squares, and the total number resting on one hundred squares

obtained. The total number of colourless corpuscles in a c.mm. of blood may be obtained as follows :—

$$\frac{\text{Total number of white corpuscles counted} \times \text{dilution of blood} \times 4000}{\text{Number of squares counted.}} = \text{Number of colourless corpuscles per c.mm.}$$

Enumeration of the Coloured Corpuscles.—This is carried out in a similar way to that for colourless blood corpuscles, except that blood is drawn up the graduated capillary pipette to the mark 1, and normal saline solution drawn up to the mark 101.

✓ **Functions of Colourless Blood Corpuscles.**—

1. They aid in the coagulation of the blood by helping in the formation of thrombogen, and even thrombokinase. It is possible that the enzymes (lipolytic and tryptic) present in the plasma are derived from certain leucocytes.

2. They aid in repair of damaged tissue, but they do not of themselves form new tissue.

3. They are the carriers of the blood stream and of the lymph stream.

(*a*) They carry foreign matter, such as carbon particles and free pigments, such as indian ink, which particles are foreign to the blood and the lymph stream, and they deposit these particles out of harm's way in the nearest lymphatic glands. In this way they are looked upon as the scavengers of the body.

(*b*) They carry fat from the bases of the columnar-striated cells over the villi of the small intestine, and travel with the fat globule through the retiform tissue of the villus to the central lacteal radical, where these cells deposit their load of fat.

(*c*) They carry glycogen possibly from the liver to the tissues. In diabetes mellitus the polymorpho-nuclear leucocytes contain more glycogen than is normally found in them.

(*d*) They probably carry particles of iron in organic combination from the cells of the liver where it has been abstracted from the disintegrated hæmoglobin, and they probably take this iron to the red bone marrow, in order that it may be used over again to form new hæmoglobin, and therefore new red blood corpuscles.

4. They kill and remove micro-organisms from the blood and the lymph streams, possibly by secreting poisons to the

micro-organisms, called bacteriolysins; and, having poisoned the micro-organisms, they then proceed to devour them (phagocytosis). This process goes on actively in the spleen pulp. It is now generally recognised that many of the fixed cells of the body, such as the endothelial cells and connective-tissue cells, also possess the power of phagocytosis.

5. In certain circumstances they aid in the formation of new red blood corpuscles in the spleen pulp, and in the red marrow of bone, where leucocytes may be seen which contain a small particle of red colouring matter. These cells are called hæmatoblasts, and it is quite possible that they utilise the red colouring matter to form new red blood corpuscles.

6. Colourless blood corpuscles reproduce chiefly by cell division, and it is generally believed that the leucocytes give rise to new leucocytes, and the lymphocytes to new lymphocytes.

The Origin of Colourless Blood Corpuscles.—The leucocytes are probably formed chiefly in the red bone marrow, and possibly in the spleen pulp, although it has been suggested that they are formed in the bone marrow and stored in the retiform tissue of the spleen. The mother cells of the leucocytes in the red marrow are large clear cells with a single nucleus, and are known as myelocytes. The lymphocytes are formed in simple lymphatic glands, in hæmal lymphatic glands, in the tonsils, in the thymus, and in the small masses of lymphoid tissue found scattered in the body. It is possible that the hyaline cells, as previously stated, are of endothelial origin.

The Chemistry of Colourless Blood Corpuscles. — White blood corpuscles contain nucleo-protein, neutral fats, the lipoids lecithin and cholesterin, glycogen, nitrogenous extractives, potash salts, and phosphates. The nuclei consists of nuclein.

The Destruction of Colourless Corpuscles.—It is probable that the worn-out white blood corpuscles are destroyed mainly in the spleen. What actually takes place is difficult to surmise, but as spleen extract is rich in the purine bases, it is thought that some of the purine, at any rate, is derived from the nucleo-protein of the white blood corpuscles, and the purine so freed is oxidised to form monoxypurine or hypoxanthine, di-oxypurine or xanthine, and tri-oxypurine or uric acid; these changes being brought about by the action of enzymes called oxidases.

Blood Platelets.—These bodies are colourless, somewhat irregular, and smaller than coloured corpuscles. Their origin is unknown. They have been regarded as follows:—

1. As true cells containing a nucleus and protoplasm, and possessed of amœboid movements.
2. As portions of leucocytes.
3. As a precipitate of nucleo-protein deposited from the plasma during cooling of the blood.

THE COLOURED BLOOD CORPUSCLES, OR ERYTHROCYTES.

In mammals the coloured blood corpuscles are biconcave discs with rounded margins. This particular shape allows for the largest amount of surface for the corpuscles; and, moreover, allows the corpuscles to readily squeeze their way through the smallest possible capillaries. In the camel tribe the coloured corpuscles are biconvex discs. The fully formed coloured blood corpuscles in mammals are non-nucleated, although originally they were nucleated cells. In other vertebrates (fish, amphibia, reptiles, and birds) the coloured corpuscles are ovoid and nucleated. The size of the corpuscles bears no relation to the size of the animal. The human coloured corpuscles are 7·7 μ ($\frac{1}{3200}$ inch)[1] in diameter and 1·9 μ ($\frac{1}{12000}$ inch) in thickness.

In man there are 5,000,000 coloured corpuscles per cubic millimetre, and about 500 coloured corpuscles to one colourless corpuscle.

The Action of Re-agents upon the Coloured Blood Corpuscles.—If blood is dropped into an isotonic salt solution—that is, a solution of the same molecular concentration and osmotic pressure as the blood plasma—the coloured blood corpuscles retain their shape. Such a salt solution, isotonic with blood plasma, is about the strength 0·9 per cent. sodium chloride solution. If the blood is dropped into a hypertonic salt solution—that is, one of greater osmotic pressure than the plasma—the salt in the solution attracts water from the corpuscles, which then become crenated. If, however, the blood is dropped into a hypotonic salt solution—that is, one of less osmotic pressure than the salt in the plasma—water diffuses into the corpuscles, and the membrane of the corpuscles becomes distended—that is, the corpuscles swell up and eventually rupture.

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[1] μ is a thousandth part of a millimetre, *i.e.* a micromillimetre.

Distilled water has the same effect as a hypotonic salt solution. If a little tannic acid or boric acid is added to blood on a glass slide, the colouring matter or oxyhæmoglobin becomes coagulated inside the corpuscle, and then is extruded. If, however, the corpuscles are nucleated (*e.g.* those of the frog), the oxyhæmoglobin usually collects into a small globule and becomes attached to the nucleus.

Chloroform and ether dissolve the lipoids, such as lecithin, which are present in the cell membrane, so that the oxyhæmoglobin escapes into the fluid outside the corpuscle.

As the blood circulates in the body, the corpuscles remain separate and distinct, but if blood is examined microscopically it is found that the corpuscles tend to stick together in the form of rouleaux.

Composition of the Coloured Blood Corpuscles. — Some physiologists consider that red blood corpuscles are composed of a soft, yielding, and elastic membrane, which encloses a fluid with the colouring matter in solution, and most probably that the oxyhæmoglobin is supported by delicate fibres forming a stroma which pervades the corpuscle and helps to maintain its shape. It may be, however, that the oxyhæmoglobin is not in solution, but loosely attached to the nucleo-protein of the stroma. Red blood corpuscles consist of oxyhæmoglobin 90 per cent., stroma 10 per cent. The stroma consists of nucleo-protein, cell globulin, the lipoids lecithin and cholesterin, and potash salts, especially potassium phosphate. The lipoids in the coat seem to protect the corpuscles and keep the contents intact. If the permeability of the envelope is interfered with, hæmolysis takes place, and oxyhæmoglobin escapes into the plasma.

The Origin of the Coloured Blood Corpuscles. — In the developing embryo there are to be found large branched connective tissue cells in the vascular area of the mesoblast. These cells are multinucleated, occur in groups, and are called angioblasts. As development proceeds the protoplasm of the angioblasts becomes continuous. Some of the protoplasm in the peripheral parts of the cells becomes fluid, forming the plasma; that nearer the nuclei becomes more solid, and surrounds the nuclei. This protoplasm develops the red colouring matter hæmoglobin, and thus nucleated red blood corpuscles are formed in this developing area. It is said that in the embryo, up to one month, all the red blood corpuscles are nucleated. Angioblasts are also found in the connective tissue towards the end of fœtal life, and it is believed that non-nucleated coloured corpuscles may be produced in these angioblasts in a similar way to the production of the nucleated cells.

In the human fœtus, towards the end of its fœtal existence, it is found that the nucleated red blood corpuscles give way to non-nucleated discs. Red blood discs may in a similar manner be formed from some of the cells in the liver. In the adult, however, it is believed that the majority of the red blood corpuscles are formed in the red bone marrow from nucleated red corpuscles, called normoblasts; but some may arise also from the hæmatoblasts, or nucleated cells containing red pigment, which are found in the spleen pulp.

The Functions of the Coloured Blood Corpuscles.—The most important substance in the red blood corpuscle is oxyhæmoglobin. This consists of hæmatin which contains iron, and a histone called globin. The chief function of the red blood corpuscles is to take up oxygen from the lungs, in some types of animals, such as frogs from the skin, and in others from the gills, and to carry the oxygen, which is combined in the hæmatin portion of oxyhæmoglobin, to the tissues, where the tissues acquire the bulk of the oxygen from the oxyhæmoglobin. Collectively the red corpuscles form a very large area over which gaseous interchange may take place; this area is called the "internal respiratory surface." The number of red corpuscles and the amount of oxyhæmoglobin in the blood seem to vary directly with the amount of oxygen needed. At high altitudes the number of red corpuscles in the blood increases, due possibly to the increased difficulty of oxygenating the blood at high elevations. The corpuscles receive from the tissues carbon-dioxide, and some of this is probably held by the globin portion of the oxyhæmoglobin, and in this way is taken back to the lungs to be excreted. It will be seen, then, that the main use of the red blood corpuscles is to aid the respiratory process. The power of holding oxygen seems to depend upon the iron contained in the hæmatin, and, moreover, as the hæmatin delivers its load of oxygen to the tissues, so the globin becomes loaded up with CO_2, which it takes back to the lungs.

The Destruction of the Worn-out Coloured Blood Corpuscles.—It is believed that the spleen is the region where the red blood corpuscles are partially, or in some cases even completely, disintegrated. It may be that this disintegration is brought about by the squeezing action of the plain muscle in the capsule and trabeculæ of the spleen, the corpuscles being caught in the splenic meshwork. Although there is no free iron in the spleen pulp, yet there is iron in organic combination with protein, and it may be that this is derived from the oxyhæmoglobin. Moreover, in the spleen pulp are found hæmatoblasts, which are nucleated cells containing a small globule of red colouring matter, which is probably derived from the oxyhæmoglobin of a coloured corpuscle. There is no appreciable amount of free oxyhæmoglobin, however, in the blood plasma in the splenic vein. It is believed that the complete chemical disintegration of the hæmoglobin is brought about by the liver cells, and here it should be noted the blood is in intimate relationship with the liver cells themselves. What exactly happens in the liver is not known, but in all probability the bilirubin and the biliverdin of the bile are derived from disintegrated hæmoglobin. At any rate, as bilirubin and biliverdin are composed of C.H.O.N., they will account for those same elements which are present in hæmoglobin; but it is also believed that the bile salts, sodium taurocholate and sodium glycocholate, are partly, at any rate, derived from protein, and in this particular instance from chromo-protein, which is hæmoglobin. Sodium taurocholate consists of the elements Na, C, H, O, N, and S. Sodium glycocholate consists of the elements Na, C, H, O, and N. It will be seen, then, that the sulphur of hæmoglobin is accounted for in the sodium taurocholate. The bile pigments and the bile salts contain no Fe, whereas hæmoglobin contains 0·4 per cent. of Fe. The liver cells store the iron in organic combination, and, in normal circumstances, the iron is taken to the red bone marrow to be utilised again in the formation of fresh hæmoglobin. In the disease, pernicious anæmia, in which there is either defective hæmogenesis, which means that there is defective formation of red blood corpuscles, or it may be, increased hæmolysis—that is, an increased destruction of red blood corpuscles, brought about by toxins which are in the blood stream—there is an increased deposit of iron in the liver cells. Iron may be demonstrated in the liver cells by one of the following methods :—

1. Small pieces of fresh liver are placed in alcohol, in which there has been previously dissolved ammonium sulphide; the alcohol hardens the tissue, and the ammonium sulphide stains the iron particles black,—that is, sulphide of iron is produced. If sections of the liver are made, these black particles can be readily seen in the liver cells.

2. *The Prussian Blue Method.*—If fresh liver is treated with ferrocyanide of potassium and a little acetic acid, and sections of it cut, it is found that the iron particles become blue.

During the destruction of the red blood corpuscles it is obvious that the stroma must be disintegrated too; the chief protein of the stroma is nucleo-protein, which is one of the precursors of the purine bodies present in the blood.

OXYHÆMOGLOBIN AND ITS DERIVATIVES.

Laky blood consists of blood serum with hæmoglobin in solution. It may be produced by any of the methods which cause disintegration of the coloured blood corpuscles. The chief methods by which it is produced are as follows :—

1. To a little blood in a test tube add distilled water, and rapidly shake. The hæmoglobin goes into solution.

2. By adding to blood, chloroform or ether, and rapidly shaking, the lipoids of the red corpuscles are dissolved, and the hæmoglobin escapes from the stroma and goes into solution.

3. A similar disintegration of the red blood corpuscles may be brought about by rapidly freezing and then thawing the blood.

4. One of the readiest methods of obtaining hæmoglobin in solution is by whipping blood; this causes the formation of fibrin, which is collected on the twigs which have been used to whip the blood, and the substance left behind consists of defibrinated blood, or, strictly speaking, blood-serum with oxyhæmoglobin in solution, the motion of the twigs having caused the red blood corpuscles to disintegrate.

Composition of Hæmoglobin.—Oxyhæmoglobin, or the respiratory protein, is a chromo-protein which consists of hæmatin ($C_{32}H_{32}N_4FeO_4$, or $C_{32}H_{30}N_4FeO_3.H_2O$) and globin, which is a histone (*vide* p. 18). Hæmoglobin in solution is dextro-rotatory. It consists of about

C	54 per cent.	N	16 per cent.
H	7 „	S	0·4 „
O	21 „	Fe	0·4 „

The proportions of hæmatin and globin contained in oxyhæmoglobin are variously given, but, as a rule, hæmatin forms 4 per cent. by weight of the oxyhæmoglobin and contains all the iron of the molecule. The histone globin forms from 86 to 94 per cent. of the oxyhæmoglobin.

The power of hæmoglobin to combine with free oxygen is due to the iron which is present.

Although hæmoglobin is a protein, it may be readily crystallised. This property of crystallisation is not characteristic of hæmoglobin only, since other animal proteins, such as serum albumin and egg albumin, have been obtained in a crystalline form, and many vegetable globulins readily crystallise.

Methods of obtaining Oxyhæmoglobin Crystals.—1. If a drop of defibrinated blood, obtained from a rat, is placed on a glass slide, and one drop of water is placed on it, and the mixture covered with a cover-glass and set aside, oxyhæmoglobin crystals separate out.

2. If a drop of Canada balsam is placed on a drop of defibrinated blood, obtained from a rat, on a glass slide, and a cover-glass superimposed, oxyhæmoglobin crystals separate out.

3. If a little defibrinated blood, obtained from a guinea-pig or rat, is shaken in a test tube with a small quantity of ether, the ether causes hæmolysis of the coloured corpuscles. If the ether extract is allowed to evaporate slowly, oxyhæmoglobin crystals separate out. Oxyhæmoglobin crystals may be readily obtained from the defibrinated blood of the rat, the mouse, the guinea-pig, and the squirrel. They may be obtained also from the blood of man, though not so readily. The crystals so obtained are characteristic. Those from the rat and man form clusters of needle-shaped crystals; those from the guinea-pig form four-sided prisms; those from the squirrel hexagonal plates. It is not understood why the different species give rise to different forms of oxyhæmoglobin crystals.

Hæmoglobin readily takes up oxygen (respiratory oxygen) from the air in the lung alveoli, and forms an unstable chemical compound oxyhæmoglobin. The tissues take up the bulk of the respiratory oxygen from the oxyhæmoglobin, but it is very questionable whether the oxyhæmoglobin is ever completely reduced, even in the last stages of asphyxia. Oxyhæmoglobin may be readily reduced, however, by artificial means; this is best done by adding to a solution of oxyhæmoglobin a few drops of *freshly* prepared Stokes' fluid (a solution of ferrous sulphate and tartaric acid made alkaline with ammonia). A solution of ammonium sulphide or hydrogen sulphide will also readily remove the respiratory oxygen from oxyhæmoglobin, producing hæmoglobin. One gramme of hæmoglobin will combine with 1·34 c.c. of oxygen.

The Derivatives of Oxyhæmoglobin.—There are certain pigments found in the body which are derived from oxyhæmoglobin, *e.g.* the bile pigments, bilirubin and biliverdin; the pigments of the urine, such as urobilin and the pigment of the fæces, as stercobilin. These normal derivatives of hæmoglobin contain no iron. There are some abnormal derivatives of oxyhæmoglobin which occur in certain diseases, such as methæmoglobin, hæmatophophyrin, hæmatoidin, and carboxyhæmoglobin. There are some pigments derived from oxyhæmoglobin which are produced artificially, namely, reduced hæmoglobin (hæmoglobin), acid hæmatin, alkaline hæmatin, hæmochromogen and hæmin.

Oxyhæmoglobin.

If a weak solution of defibrinated blood is examined with a spectroscope, two absorption bands will be seen which are placed between the D and E lines of the spectrum. The absorption band near the D is well defined and narrow. The absorption band near the E is less defined and broader. If the photographic spectrum is examined, it will be seen that there is a narrow absorption band near the violet end of the spectrum, that is between the G and H lines; this is known as Soret's absorption band.

Hæmoglobin.

This substance may be produced by adding a few drops of freshly prepared Stokes' fluid to a solution of oxyhæmoglobin. One fairly broad, somewhat ill-defined, absorption band is seen between the D and E lines, and a Soret's absorption band between the G and H lines, but the Soret's

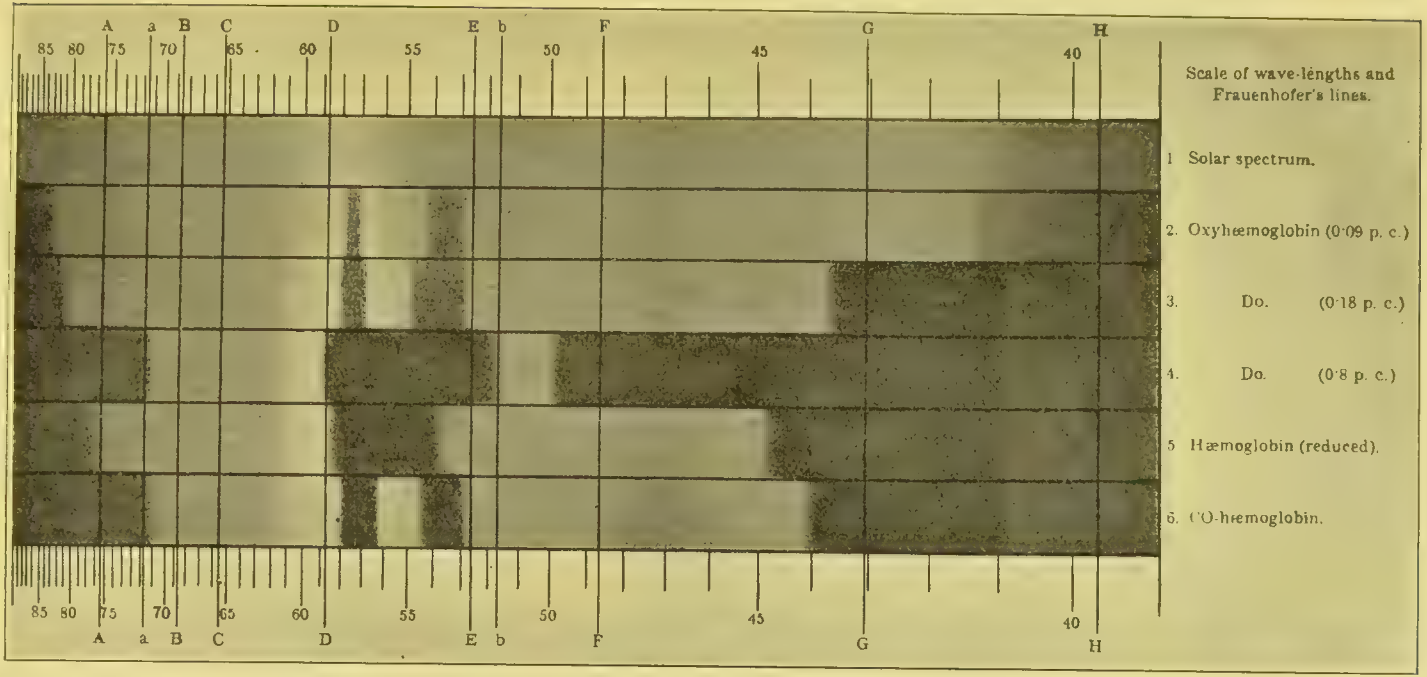


FIG. 35.—Spectra of oxyhæmoglobin and its derivatives. (Gibson and Russell.)

band is nearer to the G line than it is in the case of oxyhæmoglobin.

Carboxyhæmoglobin.

This may be produced by allowing coal gas to bubble through a solution of oxyhæmoglobin. It is produced in the blood in cases of coal gas poisoning. Carbon monoxide is present in coal mines after an explosion; this is due to incomplete combustion. Miners in a mine explosion generally die through being poisoned by this gas. The carbon-monoxide combines in a very stable manner with the oxyhæmoglobin, replacing the whole of the oxygen; that is to say, the hæmoglobin can no longer hold oxygen because it is saturated with carbon-monoxide. Carboxyhæmoglobin is not readily dissociated. In coal gas poisoning the tissues are deprived of oxygen, and death follows from asphyxia, though the tissues remain pink or cherry red. The appropriate treatment for a case of coal gas poisoning, therefore, is to perform artificial respiration, and make the patient inhale pure oxygen under pressure in order that the blood plasma may be induced to take up sufficient oxygen to keep the tissues alive for the time being. At the same time, it is necessary to keep the patient warm in order that metabolism may be kept up and the nerve centres excitable. Carboxyhæmoglobin, in dilute solutions, gives a cherry red colour, whereas a solution of oxyhæmoglobin gives a dull red colour. Carboxyhæmoglobin produces two absorption bands between the D and E lines of the spectrum, a narrow well-defined line near the D, and a broader less defined line towards the E. The narrow line is farther away from the D line towards the violet end of the spectrum than is the narrow band in the case of oxyhæmoglobin. There is also a Soret's band between the G and H lines, in a similar position to the Soret's band which is present in the spectrum of hæmoglobin.

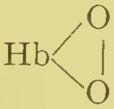
Nitroxyhæmoglobin.

This substance is produced by first adding ammonia to the defibrinated blood, and then passing nitric oxide through the solution. Its spectroscopic appearance is the same as that of carboxyhæmoglobin. Nitroxyhæmoglobin, however, seems to be even a more suitable compound than carboxyhæmoglobin. Carboxyhæmoglobin and nitroxyhæmoglobin form crystals like those of oxyhæmoglobin.

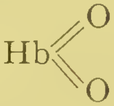
Methæmoglobin.

This substance may be produced by adding to a solution of oxyhæmoglobin a few drops of ferricyanide of potassium, and then gently warming the mixture. It may be produced by adding, in a similar fashion, a few drops of potassium permanganate or nitrite of amyl. The ferricyanide of potassium turns out all the respiratory oxygen from oxyhæmoglobin, and then yields up to the hæmoglobin oxygen in equal amount from the salts of the blood, so that methæmoglobin actually contains as much oxygen as oxyhæmoglobin does, only it is differently combined.

The condition of the oxygen in oxyhæmoglobin may be represented thus:—



Whereas in methæmoglobin (as representing a more stable compound) it is represented thus:—



Methæmoglobin produces a brownish red solution, and, when examined with the spectroscope, gives one well defined absorption band between the C and D lines, and a Soret's band between the G and H lines. Sometimes in the body some of the oxyhæmoglobin is decomposed by poisons, and as a result methæmoglobin is produced, probably in the liver, and is excreted by the cells of the renal tubules. It therefore occurs in the urine (methæmoglobinuria). Methæmoglobin in the urine occurs in certain fevers, and may also be brought about by the administration of certain drugs, such as antifebrin, phenacetin, and large doses of potassium chlorate.

Acid Hæmatin.

If a few drops of a solution, consisting of absolute alcohol 150 c.c. with concentrated sulphuric acid 6 c.c., are added to a solution of oxyhæmoglobin, acid hæmatin is readily produced. It gives one well-defined absorption band between the C and D lines of the spectrum. There is no Soret's band. Acid hæmatin solution is obviously acid; methæmoglobin solution is, as a rule, alkaline, and so these two may be readily distinguished, although they both give rise to a single well-defined absorption band between the C and D lines of the spectrum.

Alkaline Hæmatin.

If a few drops of a solution, consisting of absolute alcohol 150 c.c. and 50 per cent. caustic potash 18 c.c., are added to a solution of oxyhæmoglobin, alkaline hæmatin is readily produced. It gives one absorption band in the neighbourhood of the D line of the spectrum. There is no Soret's band.

Hæmochromogen (reduced Alkaline Hæmatin).

If a few drops of freshly prepared Stokes' fluid are added to a solution of alkaline hæmatin, hæmochromogen is formed. It gives two absorption bands, a dark one midway between the D and E lines, and a less defined absorption over the E. There is no Soret's band. The spectroscopic appearance of hæmochromogen can be readily seen even in weak solutions; and this renders the formation of hæmochromogen an extremely useful test for blood pigment. The suspected pigment is dissolved in caustic potash, and then Stokes' fluid is added.

Acid Hæmatoporphyrin.

This substance has the composition $C_{16}H_{18}N_2O_3$, and may be prepared as follows:—

Into a test tube should be put about three-quarters of an inch of concentrated sulphuric acid, and on to it one drop of undiluted defibrinated blood. The test tube should be gently shaken, acid hæmatoporphyrin is produced, and goes into solution in the sulphuric acid. It is of a maroon colour. The concentrated sulphuric acid, like other acids, breaks up the oxyhæmoglobin into globin and acid hæmatin; but the sulphuric acid goes further and abstracts the iron, so that there is produced iron-free acid hæmatin, which is acid hæmatoporphyrin. Hæmatin may be similarly decomposed by hydrobromic acid with the resulting formation of hæmatoporphyrin, thus—

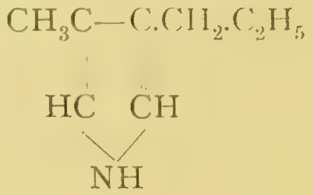
$$\underset{\text{(Hæmatin)}}{C_{32}H_{22}N_4FeO_4} + 2H_2O + 2HBr = \underset{\text{(Hæmatoporphyrin).}}{2C_{16}H_{18}N_2O_3} + FeBr_2 + H_2.$$

Acid hæmatoporphyrin gives one narrow absorption band between the C and D lines, and a darker absorption band between the D and E lines. There is also a Soret's band in the violet end of the spectrum.

Alkaline Hæmatoporphyrin.

This is produced in a similar manner to acid hæmatoporphyrin; only, into the test tube should be put first a strong solution of caustic potash. The potash breaks up the oxyhæmoglobin into globin and alkaline hæmatin, but the potash abstracts the iron from the alkaline hæmatin, producing iron-free alkaline hæmatin, or alkaline hæmatoporphyrin. Alkaline hæmatoporphyrin, as a rule, gives four absorption bands, one narrow band between the C and D lines, two narrow bands between the D and E lines, and a darker, broader band between the E and F lines. There is a Soret's band. Sometimes hæmatoporphyrin occurs in the urine (hæmatoporphyrinuria), the variety which is found is the alkaline type, for, although it occurs in the acid urine, it is produced in the alkaline blood. This condition is produced by certain poisons, such as sulphonal and trional, and when it occurs it is a serious condition. The acid variety of hæmatoporphyrin may be readily obtained from the urine in the case of alkaline hæmatoporphyrinuria by adding a little sulphuric acid.

It has been noted that hæmoglobin is called respiratory protein or respiratory pigment. The respiratory pigment in plants is chlorophyll, and there seems to be a near relationship between these two colouring matters. Hæmatoporphyrin has the following formula—$C_{16}H_{18}N_2O_3$; this is also the formula for bilirubin. Chlorophyll, if treated with alcoholic potash at 190° C, gives rise to a substance called phylloporphyrin, of which the formula is $C_{16}H_{18}N_2O$. Phylloporphyrin forms a blood red solution and may be crystallised. Both hæmatoporphyrin and phylloporphyrin, on reduction, give rise to a substance called hæmopyrrol, or methyl-propyl-pyrrol, which has the following formula :—



Hæmin.

This is an artificial derivative of oxyhæmoglobin, and may be produced as follows :—

One drop of fresh blood is placed on a slide and set aside to dry. When dry a drop of glacial acetic acid is added. The whole is covered with a cover-glass, and the glass slide heated (not boiled) over the flame of a spirit lamp. On cooling, hæmin crystals separate out; these are small dark elongated crystals, usually separate, but occasionally in groups of twos and threes. If stale or dried blood is used for the formation of hæmin, one crystal of sodium chloride must be added to the blood before the glacial acetic acid is applied.

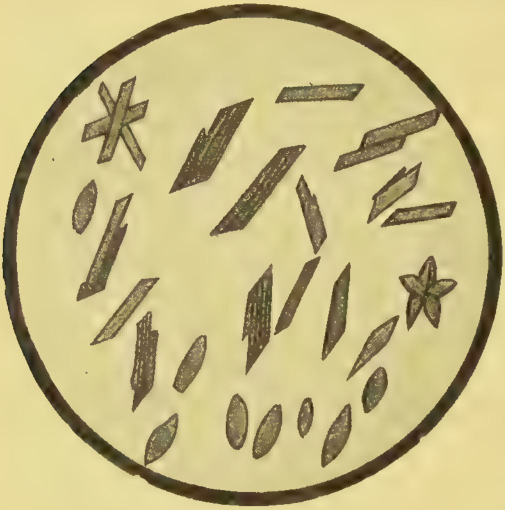


FIG. 36.—Diagram of hæmin crystals. (R. J. M. Buchanan.)

The chemistry of the change which takes place is probably as follows :—

The acid breaks the oxyhæmoglobin into acid hæmatin and globin. The glacial acetic acid combines with the sodium chloride to form sodium acetate and nascent hydrochloric acid. The nascent hydrochloric acid acts upon the acid hæmatin to form hydrochloride of hæmatin, or hæmin, and the crystals so obtained are called Teichmann's crystals.

$$\underset{\text{(Hæmatin)}}{C_{32}H_{32}N_4FeO_4} + HCl = \underset{\text{(Chlorhæmatin or Hæmin)}}{C_{32}H_{31}ClN_4FeO_3} + H_2O$$

Hæmin gives no absorption bands.

Hæmatoidin.

This forms flat lozenge-shaped crystals, and is found in the neighbourhood of old blood clots, or hæmorrhages which have occurred in the body, particularly in the brain or the lungs. It gives no absorption bands with the spectrum, and is iron free. Bilirubin, biliverdin, the colouring matters of the bile, and urochrome, the chief colouring matter of the urine, are all iron free, and give no absorption bands.

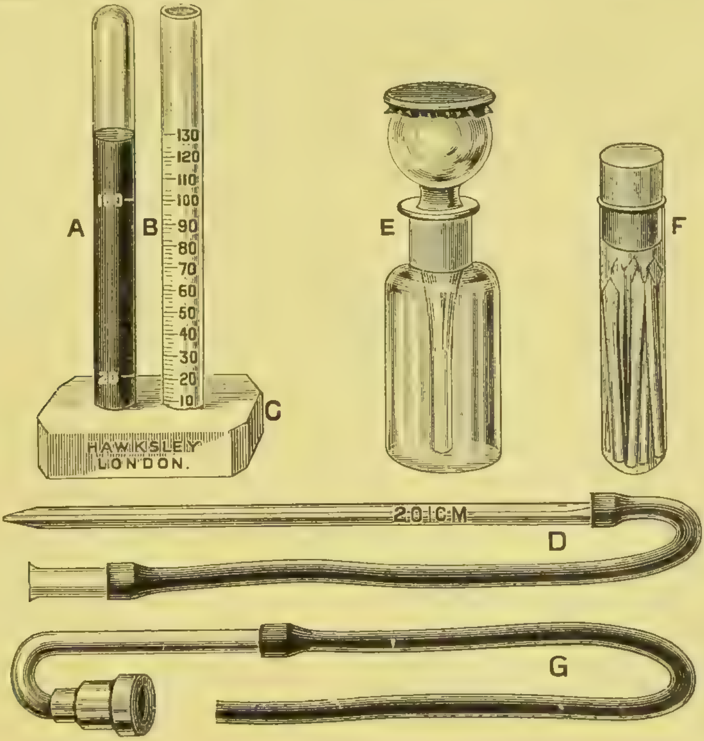


FIG. 37.—Haldane-Gowers' hæmoglobinometer. (Buchanan.)

A = Glass tube containing blood solution of standard tint (a 1 per cent. solution of blood containing the average percentage of hæmoglobin found in the blood of healthy men, saturated with CO).
B = Graduated tube.
C = Rubber stand for tubes *A* and *B*.
D = Capillary pipette and suction pipe.
E = Glass bottle with pipette stopper.
F = Glass tube holding six lancets.
G = Tube and cap for fixing over ordinary gas-burner.

THE ESTIMATION OF THE AMOUNT OF HÆMOGLOBIN.

This is carried out by a hæmoglobinometer. One frequently used is Haldane's modification of Gowers' hæmoglobinometer. The standard for comparison of the colour is contained in a sealed tube, and consists of a solution of carboxyhaemoglobin A small bottle is filled with water, and this is saturated with CO by bubbling coal gas through it for some minutes. A finger or ear lobule is pricked, and 20 c.mm. of blood are allowed to run into the capillary pipette. This is blown into the graduated tube, and diluted and shaken with the CO water added drop by drop from the bottle by the pipette stopper until the tint of the diluted blood is the same as the standard. The percentage of hæmoglobin may then be read off on the graduated tube.

The Iron in the Blood.

Hæmoglobin contains 0·4 per cent. of iron. It is calculated that the whole blood of an average sized man contains only 2·5 grs. of iron. The iron of the blood is derived from the food. The compounds in the food which contain iron are called hæmatogens. These substances are allied to nucleoproteins, and are chiefly derived from vegetable food, but a compound called hæmatogen was first prepared by Bunge from the yolk of eggs. Iron in the body is a very precious metal, and, as already pointed out, when the hæmoglobin is destroyed in the liver, the iron is not excreted, but retained by the liver cells, and is probably used over again in the red marrow of bone to help to form fresh hæmoglobin for new red blood corpuscles. The pigments of the bile, of the urine, and of the fæces contain no iron. Bile, however, contains a very small amount of phosphate of iron. It is said that the capacity which the hæmoglobin has for holding and carrying the respiratory oxygen depends directly upon the percentage of iron present.

THE BLOOD AS A PHYSIOLOGICAL PROTECTION AGAINST DISEASE.

The Antibodies, Immunity, etc.

Most, if not all, protein substances when injected into the blood or tissues of animals in which they do not occur normally, lead to the appearance in the blood of other substances, called *antibodies*, which are also proteins, and which have the power of combining with, and modifying the properties of, the substances which caused them to be produced. These antibodies are termed *antigens*, and are classified according to the nature of their antigens and of the alterations in the properties of the latter which they cause.

1. **Antitoxins.**—Here the antigens are poisonous substances of unknown chemical composition, but apparently allied to the enzymes, and formed by certain bacteria, such as the bacilli of diphtheria and tetanus. These, when injected in suitable doses into a horse or other animal, lead to the production of antibodies which neutralise their toxins and render them innocuous. These substances are *specific*, *i.e.* tetanus antitoxin will neutralise tetanus toxin, but not that of diphtheria. The antitoxin to the toxin of diphtheria is prepared on a large scale by repeated injections into horses of a potent toxin, and it is of enormous value in the treatment of the disease (diphtheria) in man.

Antitoxins against animal poisons (such as snake venom or venine), and those of the higher plants (ricin, abrin, etc.), may also be prepared provided that the poisons are protein in nature.

2. **Antienzymes** can be prepared in a similar way to antitoxins. Antitrypsin occurs in the blood naturally: its origin and function are at present unknown.

3. **Precipitins** are antibodies called forth by the injection of coagulable proteins into suitable animals. They have the power of precipitating these proteins (their antigens). For example, if a solution of pure recrystallised egg-albumin is injected into a rabbit, and after a week or so the animal is bled, it will be found that its blood serum, if mixed with a solution similar to that previously injected, will cause it to become turbid, and after a time a precipitate will settle to the bottom of the test-tube, leaving a clear supernatant fluid; solutions of other albumins and of globulins will be unaffected. A rabbit treated with two or three injections of human blood serum will develop a precipitin for that substance. This is very nearly specific. It precipitates human serum strongly, monkey's serum slightly, and that of animals more remote biologically, little if at all. This is the basis of the "biological test" for human blood. It is extremely delicate, reacting with extremely minute traces of blood, even if old and dried.

4. **Agglutinins.**—These are exactly similar to precipitins, except that their antigens are contained in cells (bacteria, spermatozoa, red blood corpuscles, etc.). The plasma of an animal, which has been injected with any of these, acquires the

property of altering the cells or bacteria, so that, instead of forming a homogeneous emulsion, they run together into clumps. For instance, if the blood serum of a person, who has recently had typhoid fever, is mixed with an emulsion of typhoid bacilli, the latter (which in the ordinary way are actively motile) will become paralysed and run together into clumps, which settle to the bottom of the tube, leaving a clear supernatant fluid free from bacteria. Traces of this property appear early in the blood of a patient during an attack of typhoid fever, and their detection forms one of the important methods for the diagnosis of that disease (Widal's reaction). In animals which have had repeated injections of bacilli, so much agglutinin may be produced that the serum, when diluted 500,000 times, or even more, will "clump" these motile bacilli.

It is not uncommon to find that the serum of one person will agglutinate the red corpuscles of another; this is attributed to a substance called *iso-agglutinin.* Rarely, and especially in disease, a person's blood serum may clump his own corpuscles; this is said to be due to the presence of *auto-agglutinin.*

5. **Cytolysins** (including *hæmolysins*, *bacteriolysins*, etc.). The blood serum of some animals will dissolve the red corpuscles from other species if the two are incubated together at body-temperature, *e.g.* human blood serum will dissolve sheep's corpuscles. This is an example of hæmolysis in normal blood. When it does not occur, it can always be produced by one or two injections of the corpuscles to be dissolved (the *antigen*) into the animal from which the serum is to be obtained. For example, the serum of the normal rabbit has no action upon sheep's corpuscles, but it acquires such a property about a week after the animal (rabbit) has been injected with an emulsion of these (sheep's) corpuscles. In a similar way the property of dissolving cholera vibrios, typhoid bacilli, and some other bacteria, after being injected ("vaccinated") with these organisms, is acquired. The main features of the phenomena are the same in hæmolysis and bacteriolysis. They are somewhat complicated, inasmuch as *two* substances are necessary. Of these only one is an antibody, the other occurs normally in the blood serum.

(*a*) The antibody is termed *amboceptor*, *immune body*, etc. It may occur naturally in the blood, as in the case of the human amboceptor to sheep's corpuscles, or it may be produced or increased in amount by injections of the cells which form its antigen. It is thermostable, *i.e.* it is not destroyed at 55° C. in thirty minutes, or at 60° C. in ten minutes. It combines with its antigen (corpuscles, cells, etc.) at 0° C. or at higher temperatures, and the substances in question are unaltered in appearance.

(*b*) *Complement* or *alexin* occurs naturally in the serum. It is thermolabile, being destroyed at 60° C. in ten minutes, or at 55° C. in half an hour. It disappears in a few days at the room temperature, but can be preserved two or three weeks at 0° C., or for longer periods in a dry state. In itself it is without action on blood corpuscles or bacteria; but when the latter have been "sensitised" by being combined with the amboceptor, it dissolves them, partially or completely. This action only takes place at or near the body temperature.

The processes of hæmolysis and bacteriolysis, therefore, may be pictured thus: The antibody (amboceptor) unites with its antigen (the corpuscle or bacterium) and renders it vulnerable to the complement, which unites either with the cell or with the amboceptor, which thus acts as a link between the two. In either case the complement exerts an "enzyme-like" action, and solution takes place.

There is no doubt that these various antibodies play a part of great importance in protecting the body against disease and in curing disease when once bacteria have gained entrance to the blood. Exactly how this is done, or what is the rôle of each substance, is not yet definitely known.

There is, however, another method by which bacteria are attacked, and this is perhaps even more important than the mechanisms already described.

Phagocytosis.—The leucocytes (especially the polymorphonuclears) and certain other cells, notably endothelial cells, have the power of ingesting and removing, and in some cases of digesting, almost any dead and inert matter which may gain access to the tissues (*vide* p. 244). Effused blood is largely removed in this way, either before or after the pigment is transformed into hæmatoidin; particles of dirt and other material are gradually absorbed, mostly by phagocytosis. A physiological example of the process may be seen in the absorption of the tail of the tadpole, which is effected by the leucocytes when the animal assumes the adult form. In disease the leucocytes may be found to contain bacteria, which may often be seen to be undergoing solution. This is undoubtedly one of the most efficacious methods by which the body combats disease, and in general terms it may be stated that the less easily a bacterium can be taken up by the leucocytes the more potent is it as a cause of disease. The process is a complex one, since in most, if not in all cases, the leucocytes have no power of attacking unaltered bacteria; these must first be "sensitised" by being combined with a substance or substances which occur in the serum and presumably in the plasma. These are termed "*opsonins*," and their nature is somewhat doubtful; probably there is a special substance having this action, and it may be that other antibodies, and perhaps also a complement, can prepare bacteria for ingestion by the leucocytes.

FORMATION OF ANTIBODIES.—The only suggestion to account for this remarkable phenomenon is Ehrlich's side-chain theory. It is briefly as follows: In any molecule of living protein two parts may be distinguished: (*a*) That which discharges the function natural to the cells of which it is a constituent, and (*b*) that which nourishes the former, more important, part. This latter, Ehrlich likens to the "side-chains" of a complicated organic substance, and imagines it to consist of separate groups of atoms, each having a specific capacity to unite with food molecules of protein, which it alters in such a way that they are built up into the living "protein-molecule." An antigen (which is always a protein) unites with a side-chain in exactly the same way, but the compound thus formed is useless to the cell, and the side-chain which has united with it is also rendered useless in nutrition. Another similar side-chain has to be produced, and if this is in its turn rendered useless by more antigen, the cell may be trained to produce more and more similar side-chains until they are formed in such numbers that they break off from the molecule and accumulate in the blood. In this region they retain their power of combining with their antigen, and form molecules of the specific antibody.

Anaphylaxis, or "hypersensitiveness."—If a small amount (as little as $\frac{1}{20.000.000}$ part of a gramme (Wells)) of a protein (which need not be poisonous to normal animals) is injected into a guinea-pig, it will be found, after an interval of one to three weeks, to be profoundly altered, so that a second injection of the same protein will cause an extraordinary group of symptoms, including tonic and clonic spasms, vomiting, and violent convulsions, accelerated pulse rate and respiratory movements, and finally death, apparently from respiratory paralysis. These symptoms come on in most cases within a few minutes of the administration of the second injection, and the animal either dies within a couple of hours, or recovers, and then is no longer sensitive to a second injection. This state of "exaggerated sensitiveness" to proteins is called *anaphylaxis*. It occurs in most other animals, including man, alarming symptoms sometimes occurring in patients who have received a second injection of diphtheria antitoxin sometime after the first injection.

TESTS FOR BLOOD.

1. *Microscopical Examination to distinguish Mammalian from Non-mammalian Blood.*

2. *Spectroscopical Examination.*—Look particularly for the absorption bands of oxyhæmoglobin. The solution should then be reduced with freshly made Stokes' fluid, and the solution examined for hæmoglobin. The hæmoglobin solution may be shaken with air, when oxyhæmoglobin will return. If the blood is present in a small quantity, it is well to prepare alkaline hæmatin, and then reduce this with Stokes' fluid, and examine carefully for the two absorption bands of reduced alkaline hæmatin or hæmochromogen; one well defined dark absorption band appears between D and E, and a lighter absorption band over the E line.

3. *The Chemical Test* for blood consists in the preparation of hæmin crystals (Teichmann's crystals, *vide* p. 262).

4. *The Guaiacum Test for Blood.*—To a little blood, or a solution containing blood (such as urine with a trace of blood), add a few drops of tincture of guaiacum; this causes a white precipitate to appear. A solution of hydrogen peroxide (or ozonic ether which contains H_2O_2) is then added; this causes a blue colour to appear. Even if the blood is previously boiled this reaction occurs, and is due to the presence of the iron in the hæmoglobin. A similar reaction is given with milk; this is due to the presence of an enzyme called peroxidase, which is, however, destroyed by boiling, and boiled milk will not give the reaction.

5. *Biological Test for Human Blood.*—(See under heading "Precipitins," p. 265).

CHAPTER XIX

INFLAMMATION

By inflammation is meant those changes which take place in a tissue which has been injured, provided that the injury has not caused the death of the tissue, *i.e.* inflammation is reaction to injury. It is looked upon as a protective process by means of which the advance of harmful micro-organisms is limited, and by the process of inflammation they are finally eliminated from the body. Many of the phenomena of inflammation may be studied in the web of the foot of a frog. The animal should first be curarised, then the web may be readily spread across an aperture made in a piece of thin cork and examined under the microscope. The following observations may be readily made:—

1. The blood flowing rapidly through the arterioles into the fine capillaries where the axial stream contains the coloured corpuscles, each separate from the other. Some leucocytes may be seen amongst the coloured corpuscles, but a few may be observed slowly moving along the wall of the capillary in the peripheral part of the stream.

2. Changes in the calibre of the arterioles due to vaso-motor influences, and in this way the capillary flow is regulated.

3. Changes in the pigment cells of the skin; these represent the perivascular connective-tissue cells. The pigment cells contract when exposed to bright light, and expand when the light is diminished.

If the skin is irritated, the early vascular changes which occur in inflammation may be observed.

Briefly, the phenomena which occur in an inflamed area may be described under two headings:

(1) The changes which occur in the blood vessels in the inflamed area.

(2) The changes which occur in the perivascular tissues.

I. Thë Vascular Changes in Inflammation.

The arterioles in the damaged area exhibit a momentary contraction; this is followed by dilatation. In consequence of this vaso-dilatation *hyperæmia* occurs, and an acceleration of the blood flow into the capillaries takes place. After a while the blood stream becomes gradually *retarded* and then *oscillates*, the massed corpuscles moving slowly forwards, then backwards, and finally a condition of *stasis*, or standstill, is reached. At this stage many of the leucocytes and coloured blood corpuscles may be observed adhering to the sides of the blood vessel, having gradually left the axial stream. Before actual inflammatory stasis occurs, the leucocytes, by means of their amœboid movements, wander out of the capillaries between the endothelial cells lining the vessel wall (*pathological diapedesis*). It may be that the leucocytes are attracted to the area where bacteria are present, because these organisms produce soluble substances for which leucocytes appear to have a great affinity. This process is called *chemotaxis*. It has already been pointed out that the leucocytes act as scavengers of the body, and it is their function to remove noxious material; in other words, they ingest the bacteria (phagocytosis). Having performed their function as scavengers, they may now wander back into the lymphatics; some of them, however, disintegrate and help to liberate the fibrin enzyme, which brings about the coagulation of the fibrinogen contained in the exuded plasma; others die and form pus cells. It may be that some of the wandering mononuclear leucocytes give rise to some of the fibroblastic cells of the new tissue formed in tissue repair. As the result of the comparatively high pressure in the arterioles and capillaries of the inflamed area, coloured corpuscles become pressed out from the blood vessels through the apertures previously made by the leucocytes. When once these corpuscles are external to the vessel they become disintegrated, and the broken hæmoglobin is scattered in the tissue and is later reabsorbed. In some cases, however, the iron of the hæmoglobin is removed, presumably by the leucocytes, and the tissue becomes stained by the iron-free compound called hæmatoidin (*vide* p. 263).

Some of the plasma also becomes extravasated from the capillaries into the extravascular tissue, where clotting takes place, fibrin (inflammatory lymph) is produced and serum is squeezed out, producing a condition known as œdema.

II. The Tissue Changes in Inflammation.

The nuclei of the local extravascular connective-tissue cells as a rule show active mitosis, which indicates that cell proliferation is taking place. At the same time, the perivascular connective tissue becomes infiltrated with polymorpho-nuclear leucocytes and lymphocytes. If the bacteria which produce the inflammation are killed, and the inflammation is brought to an end, repair of the tissue follows. The masses of round cells (*i.e.* proliferated connective-tissue cells, leucocytes, and lymphocytes) become infiltrated by large oval cells called fibroblasts, which give rise to new fibrous tissue. These fibroblasts are in all probability derived from pre-existing extravascular connective-tissue cells and also from some of the leucocytes.

One of the commonest causes of inflammation is the invasion of the body by micro-organisms. If the invasion is a local one, then there is as a result a local inflammatory reaction; if the invasion is a general one, then there is a general inflammatory reaction. There are, however, provided in the body certain defensive arrangements against the invasion of micro-organisms. There appear to be three lines of defence against such invading parasites. The first line of defence of the body resides in the epithelial and subepithelial tissues of the skin, alimentary canal, and respiratory tract, etc. "It is interesting to note, as shown long ago by Lord Lister, that where the epithelium lining a canal, the sides of which are normally in contact, is intact and healthy, bacteria cannot spread along that canal. This is true in the case of many ducts, such as the urethra, the mammary ducts, the salivary ducts, etc., and Lord Lister used to point to this as a proof of the vital power of the tissues in preventing the growth of bacteria" (Watson Cheyne).

The second line of defence is in all probability in the lymphoid tissue and lymphatic glands, which are situated deeper than the sub-epithelial connective-tissue cells.

The third line of defence appears to be the colourless blood corpuscles contained in the blood stream, the blood plasma, and the endothelial lining of the blood vessels.

SECTION V.

CHAPTER XX.

THE HÆMOPOIETIC ORGANS.

HÆMOLYMPH GLANDS.

THE hæmopoietic organs of the body are those in which the coloured and colourless corpuscles of the blood are formed; they include simple lymphoid tissue, such as occurs in the tonsils, in the naso-pharynx, in the wall of the stomach (in some animals), and in the wall of the small and large intestine (Peyer's patches and solitary glands), the simple lymphatic glands, the hæmolymphatic glands, the spleen, the thymus, and the red marrow of bone.

There are two types of hæmolymph glands in the body:—

1. **Hæmal Glands,** which contain sinuses into which the blood is poured, thus bringing the blood into intimate relationship with the gland tissue. The spleen is an example of such glands.

2. **Hæmolymphatic Glands.**—These are lymphatic glands which have an afferent and efferent lymphatic vessel as well as an artery distributed to, and a small vein leaving, them. In these hæmolymphatic glands there are sinuses in which the blood and the lymph mix.

The hæmolymph glands are redder than ordinary lymphatic glands.

The Spleen.

The spleen is practically covered by a serous coat, beneath which is a fibrous coat which contains a little white fibrous tissue, yellow elastic tissue, and, relatively, a large quantity of plain muscle fibres. From this coat trabeculæ, which also contain plain muscle, run into the spleen substance and branch to help to form the spleen pulp, or the medullary part of the spleen. The cortical part of the spleen is converted into compartments by the trabeculæ which traverse it. These compartments consist of a network of triangular branching cells, in the meshwork of which are lymphocytes. Running in the trabeculæ are the arterioles, the sheaths of which are continuous with the trabeculæ. Where these blood vessels branch are found masses of lymphoid tissue in nodular form, which are called Malpighian follicles. The arterioles break up into fine capillaries in the centre of the Malpighian follicles. The arteries end in an open brushwork of capillaries, and the coats of the arteries are replaced by lymphoid tissue, so that the blood comes in contact with the tissue elements of the spleen. In the medulla or pulp of the spleen are large branching cells in the meshwork of which are the various forms of colourless blood corpuscles, red blood corpuscles, and hæmatoblasts, which are large nucleated cells containing little granules of colouring matter. In the medulla of the spleen are venous spaces from which the splenic vein starts. At the hilum of the spleen is the splenic artery, breaking up into its branches, the sympathetic nerves, the tributaries of the splenic vein, and lymphatic vessels.

The Development.—The spleen is developed from mesoblast in close connection with the pancreas. It appears during the first two months of the life of the human embryo, and grows slowly; the Malpighian follicles are the last parts to develop. It is intimately related to the vascular system.

The Chemistry of the Spleen.—The spleen contains 70 per cent. of water and 30 per cent. of solids. During life it is distinctly alkaline, but soon after death it becomes acid, due to the formation of sarcolactic acid. The proteins present are nucleo-protein, cell globulin, and iron in organic combination with albumin.

The extract contains fatty acids, such as formic acid, acetic acid, butyric acid, and the two lipoids cholesterin and lecithin. Besides these, in the extract of the spleen, there are hypoxanthine and xanthine, uric acid, a little glycogen, and a trace of inosite. Spleen extract is rich in sodium salts.

Experiments on the Spleen.—In animals, after the spleen has been removed, it is found that there is an increase in the hæmolymphatic glands of the body and in the red marrow of bone, which suggests that these are the organs which are capable of taking on some of the functions of the spleen.

If the spleen is placed in a plethysmograph, it is found that it exhibits rhythmical contractions which consist of *splenic systole* and *splenic diastole*. These occur about once a minute, and continue even after division of the nerves to the spleen, which leave the spinal cord in the lower thoracic anterior nerve roots, the cell station of which is in the sympathetic nerve chain or the semilunar ganglia. If the nerves to the spleen are intact, and the upper cut end of any large nerve, such as the sciatic or the vagus, is stimulated by a Faradic current, it is found that there is a reflex contraction of the blood vessels in the splanchnic area, and the spleen therefore becomes smaller. If the nerves going to the spleen are cut, the spleen becomes larger through vaso-dilatation, and if the peripheral cut end of the nerves is stimulated by a Faradic current the spleen becomes smaller. If a solution of albumose is injected into the blood stream of an animal, it will be found that the spleen volume is increased through vaso-dilatation; and if suprarenal extract is injected into the blood stream, the spleen becomes smaller through vaso-constriction. It has been observed that, during active digestion, the spleen remains small, and that, during starvation, or when digestion is not going on, the spleen becomes larger. From the structure, the physiological chemistry, and the phenomena observed after experiments performed upon it, it is surmised that the spleen has the following functions:—

1. CONCERNING THE RED BLOOD CORPUSCLES.—Since the spleen pulp contains hæmatoblasts, it is thought that, in certain circumstances, these cells may give rise to new red blood corpuscles. But the spleen has some action in the disintegration of the worn-out red blood corpuscles. Possibly, when it contracts it squeezes the red blood corpuscles which are in the meshwork of retiform tissue, and those which resist the squeeze go on in the circulation and carry on their normal function. Those which cannot resist the squeeze may be partially disintegrated, and it is quite possible that the protein containing iron, which is found in the spleen pulp, is derived from hæmoglobin. There is, however, practically no free hæmoglobin in the plasma of the splenic vein.

2. CONCERNING THE COLOURLESS BLOOD CORPUSCLES.—It may be that many of the leucocytes of the blood are derived from other leucocytes in the spleen, and that lymphocytes are formed in the Malpighian follicles; but a theory has been

advanced that leucocytes are formed only in the red marrow of bone, and that they are simply stored in the spleen pulp. The extract of spleen is rich in hypoxanthine and xanthine, and there is also some uric acid present; and it is believed that these purine bodies are derived from the nucleo-protein, which is the most important protein of the colourless blood corpuscles. That is to say, the spleen may have a function in chemically disintegrating the used colourless cells of the blood.

3. Nitrogenous Katabolism.—If hypoxanthine and xanthine are injected into the splenic artery, the splenic vein will be found to contain an increase of uric acid. The conclusion drawn, therefore, is that the hypoxanthine and xanthine are oxidised in the spleen pulp to uric acid, and that normally the uric acid which is formed in the spleen is due to the oxidation of purine bodies, derived from nucleo-protein, which is derived from the broken-down white blood corpuscles. This oxidation is due to the action of enzymes called oxidases.

4. It has been stated that contraction of the spleen takes place rhythmically. This is due to the large amount of unstriped muscle which it contains.

This contraction helps to clear the blood out of the venous spaces in the spleen, and in a way acts like a force pump, helping to propel the blood along the splenic vein through the portal vein. In this way the spleen contraction no doubt aids the portal circulation. It has been stated that during active digestion the spleen remains small. Now, this contraction of the spleen must cause some slight impediment to the blood flowing into the spleen from the splenic artery. In this way the blood, which normally comes through the splenic artery, is turned aside through the vasa brevia and the gastro-epiploica sinistra to flush the fundus region of the stomach with arterial blood, and no doubt in this way to increase the activity of the gastric glands, and therefore to aid gastric digestion. In a similar way the blood is turned aside through the arteriæ pancreaticæ parvæ and the arteria pancreatica magna, so the pancreas is flushed with more arterial blood, which must obviously increase the activity of the cells of the acini, and in this way increase pancreatic secretion. The spleen then aids, in a mechanical way, both gastric and pancreatic digestion.

5. In most infectious diseases, when micro-organisms and their toxins are present in the blood stream, the spleen is found to be somewhat enlarged; this occurs especially in typhoid fever. In many of these diseases the bacteria which cause the disease have been found in the spleen, and it has been suggested that the spleen thus acts as a kind of "blood filter," and that here the micro-organisms are more readily attacked by the massed leucocytes. Phagocytosis is known to occur actively in the spleen.

The Thymus Gland.

In the new-born child the thymus gland is of a pink colour, and consists of two lobes, the main portion of which is in the thorax, the smaller portion in the neck. The deep surface of the gland lies over the upper part of the pericardium. The thymus usually attains to its maximum of development at the end of the second year; for a time it may remain stationary, or slowly diminish in size. As a rule, at puberty it rapidly degenerates, and becomes infiltered with fat. Waldeyer has shown that, throughout life, some of the original thymus tissue usually remains. The thymus gland has an arterial supply from the inferior thyroid and internal mammary arteries, and has a large venous and lymphatic drain.

Structure.—The thymus is surrounded by a fibrous capsule which gives rise to trabeculæ, which contain the blood and lymph vessels. The trabeculæ run into the gland substance and divide the lobes into lobules. Each lobule consists of follicles of lymphoid tissue. The follicle consists of two portions,—the outer part, or cortex, consists of retiform tissue with lymphoid cells very closely packed in; the inner part, or medulla, consists of a coarse retiform matrix with fewer lymphoid cells. In the medulla are the concentric corpuscles of Hassall. These consist of a central granular nucleated cell with flattened epithelial cells concentrically arranged.

Development.—In mammals it is developed as a bilateral tubular prolongation backwards from the hypoblast of the third and a small piece of the fourth visceral clefts. The tubes are surrounded by mesoblast, which gives rise to the lymphoid cells. The lower ends of the tubes give off solid acini. Some of the original epithelium from the hypoblast remains broken up into epithelial nests, which form the concentric corpuscles of Hassall.

Chemistry.—During life the reaction is alkaline. After death it soon becomes acid (sarcolactic acid). The chief protein present is nucleo-protein; it also contains much adenine ($C_5H_3N_4.NH_2$, amino-purine), guanine ($C_5H_3N_4.NH_2.O$, amino-oxypurine), hypoxanthine ($C_5H_4N_4O$, monoxypurine), and xanthine ($C_5H_4N_4O_2$, dioxypurine).

Experiments.—Henderson has shown that castration in cattle delays the normal atrophy of the thymus; and Paton found that removal of the thymus in guinea-pigs hastens the growth of the testes and ovaries.

Function.—The exact function of the thymus has not been ascertained, but Beard regards the thymus as the starting-point of the lymphoid tissue of the body, and therefore of the lymphocytes. The masses of lymphoid tissue which form in various parts of the body are started locally by lymphocytes, which have originally come from the thymus gland, and as these secondary masses develop so the thymus itself gradually atrophies.

In the condition called "lymphatism," or "status lymphaticus," the thymus is found to be much enlarged, and the other lymphoid tissue, such as the lymphatic glands, Malpighian bodies of the spleen, the lymphoid tissue in the wall of the intestine, are all hypertrophied. The subject of this disease is an infant or young adult. The condition is one cause of sudden death, especially during anæsthesia; and both chloroform and ether seem to be equally dangerous in this disease. The cause of this sudden death is syncope, or cardiac failure, but how it is brought about is at present a mystery.

The Red Bone Marrow.

Red bone marrow is found in the cancellous tissue at the end of the long bones, and also in the cancellous tissue in the smaller bones and in the ribs. In children it is also found in the middle of the long bones, but in adults it is replaced by yellow bone marrow. If in adults there is an increased demand for red corpuscles through abnormal destruction, the red marrow at the ends of the long bones encroaches upon and replaces the yellow marrow "until the whole interior of the bone becomes a manufactory of red corpuscles." Red bone marrow consists of a reticulum of triangular branched cells. Some of these are solid with fat, the protoplasm and the nucleus being pushed to one side. Traversing the reticulum are arterioles and venules. There is an open communication between the arterioles and the venules in the interstices of the tissue, but there is no distinct interstitial circulation of blood as occurs in the spleen. In the reticular tissue are to be seen two kinds of marrow cells (*myeloplaxes*).

1. **Large Branching Cells with many Nuclei collected in the centre of the Protoplasm.**—The protoplasm is somewhat granular. These are the myeloplaxes of Robin.

2. There are other large cells, each with a single large nucleus, near which may be one or more centrosomes; occasionally a budding process of protoplasm may be seen. This is the other variety of myeloplaxe.

3. There are also cells each with a small globule of red colouring matter, presumably hæmoglobin. These are the hæmatoblasts.

4. There are cells each containing a central nucleus with the protoplasm around having a distinct red tint; these are nucleated red blood corpuscles, and are called erythroblasts or normoblasts; they give rise to non-nucleated red blood corpuscles.

5. There are also present the various varieties of leucocytes.

6. There are also the ordinary non-nucleated coloured corpuscles or erythrocytes.

The chief function of the red marrow of bone is to give rise: (1) to all the coloured corpuscles formed in the adult; (2) to the leucocytes; and, through the lymphoid tissue which it contains, (3) to many of the lymphocytes which are present in the blood.

CHAPTER XXI.

INTERNAL SECRETIONS.

INTERNAL secretions are complex substances produced by various cells of the body. They are carried away from the organ where they are formed by the lymph and venous blood stream, and are taken to other parts of the body, where they exercise their specific and stimulating action. Claude Bernard first originated the theory of the internal secretions of the different organs, and Brown-Sequard applied the theory more especially to the extracts of the testis and the ovary. Starling suggests the term "Hormone" (ὅρμαω, "I excite") for these internal secretions. The following is a list of some of these important substances :—

Hormone.	Origin.	Reacting Organ.
Iodothyrin (thyroidine)	Thyroid gland	Nervous system, skin.
Adrenalin, or Epinephrin	Medulla of the supra-renal gland	Terminations of the vaso - constrictor nerves.
A hormone which influences carbohydrate metabolism	Pancreas, possibly from the cell islets	Liver cells (?), tissue proteins (?).
Gastric secretin, or Gastrin	Pyloric glands of stomach	Fundus glands of stomach.
Secretin	Duodenal and jejunal mucous membrane	Cells of pancreas and of liver.
...	Ovary	Uterine mucous membrane and mammary gland (?).
...	Testis	Body generally.
...	Fœtus	Mammary gland.
...	Posterior lobe of pituitary body	Peripheral arterioles.

The chief features of the hormones are as follows :—

1. They have a comparatively small molecular weight.

2. Unlike enzymes, they are not destroyed by raising the temperature, but usually lose their power on prolonged boiling.

3. They are rapidly destroyed by oxidising agents.

4. They seem to be destroyed, probably by being oxidised by means of oxidases, in the tissues which they excite, and do not escape in the excretions.

5. They are not, as a rule, absorbed unaltered from the alimentary canal, except iodothyrin, and it has been suggested that this exception exists because the thyroid gland originally discharged its secretion into the alimentary canal by the thyro-glossal tract.

THE THYROID GLAND.

Structure.—The thyroid gland consists of two lobes joined by an isthmus. The thyro-glossal tract, in the fœtus, runs from the left side of the isthmus up to the foramen cæcum, at the base of the tongue. In the adult, remnants of the thyro-glossal duct persist in the pyramidal lobe of the thyroid and the levator glandulæ thyroideæ. Around the thyroid gland is a dense capsule of areolar tissue, from which fibrous trabeculæ run into the gland. The gland consists of blind vesicles surrounded by cubical cells, each containing a colloid material. In the loose connective tissue are many blood vessels, lymphatics, and nerves. The internal section leaves either by the lymphatics or by the veins.

The development of the thyroid gland is important. It consists of two portions,—one a middle diverticulum, which grows down from the pharyngeal hypoblast which is opposite the ventral ends of the second visceral arches. This portion forms the thyro-glossal tract of His and the foramen cæcum. There are two lateral diverticula; one on either side, developed from the region of the fourth visceral cleft.

Composition of Thyroid Extract.—Fresh thyroid extract is alkaline, but if the extract is obtained some time after death it is acid, due to the presence of sarcolactic acid. Thyroid substance contains water, 82 per cent.; solids, 18 per cent. The solids consist of nucleo-protein and iodothyrin (thyro-iodine). The latter substance constitutes about 10 per cent., and contains the elements C, H, O, N, P, and I. The iodothyrin is contained in the colloidal substance, which is derived from the granules in the cubical cells lining the thyroid vesicles.

Iodothyrin has been obtained as a brown amorphous substance which is soluble in weak alkalies, but almost insoluble in water. The amount of iodine present varies in different animals, and is said to be absent in cattle.

Function of the Thyroid Gland.—The knowledge of the function of the thyroid gland has been obtained by experiments on animals. If the thyroid gland is removed from a healthy dog, death, as a rule, occurs in a few days, and the following symptoms may be noted before it takes place: Tremors, spasms, and convulsions of the muscles of the body, swelling of the conjunctivæ, and a general derangement of the working of the central nervous system. This sometimes may be prevented, however, by engrafting a portion of fresh thyroid beneath the skin of the neck, or into the peritoneal cavity of the animal. If the thyroid gland is removed from a monkey two sets of phenomena may be observed: (1) nervous, and (2) metabolic. The nervous phenomena consist of tremors of the voluntary muscles and clonic and tonic spasms. The movements of the animal are, however, for the most part slow. The metabolic symptoms consist of a swelling of the loose connective tissue of the skin with diminished cutaneous sensibility, the skin becomes dry, the epithelium exfoliates, and the hair falls out. The temperature becomes subnormal. Death frequently takes place within fourteen days, before some of these later symptoms occur. If, however, the animal is kept warm it may live for seven or eight weeks. These phenomena have not been observed in birds; this is probably due to the fact that they have accessory thyroid glands. The diseased thyroid gland has been completely removed in man, and the symptoms which have followed have been both nervous and metabolic. The condition produced is called cachexia strumipriva, or operative myxœdema.

Cretinism.

Children occasionally develop a cystic condition of the thyroid gland, which ends in its enlargement and interferes with its function; or, on the other hand, the gland may be ill-developed or may even be absent. In such cases two sets of phenomena arise: mental and metabolic. The mental phenomena are those including idiocy and imbecility. The children so affected are usually stunted in growth, and frequently develop swellings about the body, particularly above the clavicles. The swellings are probably due to a degenerative condition in the loose connective tissue of the skin. As a rule the temperature becomes subnormal, and the output of nitrogen in the urine is said to be diminished.

Myxœdema.

This is a disease in which katabolic changes seem to undergo a *partial arrest.* The disease, which occurs in middle-aged persons, is associated with progressive atrophy of the thyroid gland. Symptoms are chiefly nervous and metabolic; the main nervous symptoms are those associated with slow speech, slow thought, slow actions; sometimes the patients become maniacal, occasionally melancholic. The main metabolic symptoms are those associated with an increase of immature connective tissue of the skin, especially about the hands and the feet, and swellings over the malar eminences, and there is often a general thickening of the lips and of the tongue. The skin becomes dry and the hair falls out, fat accumulates in the body. The temperature becomes subnormal because of less oxidation in the tissues, and the nitrogen output in the urine is diminished. There is an increase in the body weight.

From these experimental and clinical facts it is concluded that the thyroid gland produces an internal secretion, which leaves the gland by the blood stream or by the lymph stream, and that this secretion has an important influence upon metabolism generally. It seems to stimulate the nutrition of the central nervous system, and it increases the rate of oxidation which takes place in the tissues.

It has been found, experimentally, that thyroid extract injected into a vein of an animal causes a slight fall of arterial blood pressure. If thyroid extract is administered to a healthy adult, it causes some appreciable dilatation of the radial artery. It also causes a loss of weight and an increased output of nitrogen in the urine through increased protein katabolism, and an increased output of CO_2 by the lungs. If, however, large quantities are given, the heart beat is accelerated and palpitation follows, but there is no increase of cardiac force. The pulse rate is obviously increased in frequency, and the patient complains of giddiness; glycosuria occasionally follows, From this it will be seen that the patient develops many of the symptoms of exophthalmic goitre. In some cases of melancholia, thyroid extract has been given as a direct stimulant to the cells of the cerebral cortex, with beneficial results. Persons suffering from myxœdema may be practically cured of their disease by the administration of thyroid extract by the mouth, given, of course, over a long period.

Accessory Thyroids.

These are present in the neck of some animals, and have exactly the same structure, and in all probability have the function, as the thyroid gland.

Parathyroids.

These small glands are found lying alongside the thyroid, and are sometimes even embedded in its substance. In structure they consist of solid columns of cuboidal cells with no central lumen. Between the columns are intervening vascular spaces and capillary networks. These glands have been removed in animals with the following results: Twitching, followed by spasms, occurs in the voluntary muscles; the legs then become paralysed, respiratory movements become increased in frequency, and death follows from exhaustion. These symptoms disappear when a saline extract of parathyroid gland is injected into a vein of the animal. It has been suggested that these glands secrete a substance which neutralises some products of metabolism which are toxic to the central nervous system. On the other hand, the function of the parathyroids may be the same as that of the thyroid gland. Forsyth thinks that the parathyroids are simply portions of the thyroid glands which have not formed vesicles, but which have assumed functional activity.

THE PITUITARY BODY, OR HYPOPHYSIS CEREBRI.

Structure.—The pituitary body consists of three portions:—

1. A small posterior lobe, which grows down from the floor of the third ventricle, and consists of a neck and body. In man the neck and body are both solid, although there are traces of a cavity in the neck. This portion of the pitui-

tary body is formed of neuroglial cells, and is invaded by epithelial cells from the pars intermedia. The secretion from these cells is probably poured into the third ventricle.

2. The pars intermedia lies in front of and invests the posterior lobe, though it is developed from the anterior lobe. It consists of cells filled with fine granules, with some colloid substance between the cells which passes via the lymphatics into the cavity of the neck of the posterior lobe.

3. The anterior lobe consists of acini, lined by large granular cells which are surrounded by capillaries derived from the pituitary branches of the internal carotid artery. The internal secretion probably passes into the circular sinus which surrounds the pituitary body.

In giants and cases of acromegaly, a disease in which the bones of the hands and feet and those of the upper and lower jaw are enlarged, the pituitary body is found to be enlarged too.

Development.—The neck and posterior lobe of the gland are developed as a down-growth from the thalamen-cephalon (which forms the third ventricle), whereas the anterior lobe is an up-growth from the buccal epiblast, which is known as the diverticulum of Rathke. It is interesting to note that the notochord extends into the basis cranii as far as the pituitary body, which is early cut off from the buccal cavity.

The Effect of Removal.—The pituitary body has been removed in cats and dogs, and, as a rule, death occurs within two weeks with the following symptoms: Muscular twitchings followed by tremors and spasms, a loss of appetite and general lassitude. The body temperature falls, dyspnœa sets in, and the animal eventually dies. The symptoms abate, however, after the injection of pituitary extract.

Injection of Pituitary Extract.—It has been found that intravenous injection of the extract of the anterior portion of the gland has no particular influence upon arterial blood pressure. The extract of the posterior portion of the gland, when injected into the jugular vein of an animal, causes a general rise of arterial blood pressure, which is due to constriction of the peripheral arterioles; this is probably brought about by a direct local action on the arterioles themselves. A second injection, following the first, produces no further rise of arterial blood pressure. There is occasionally a slowing of the heart. The arterioles of the kidney, however, dilate, as is shown by an increase in kidney volume, and this vaso-dilatation is accompanied by diuresis. It should be noted that intravenous injection of adrenalin produces a rise of arterial blood pressure, a second injection produces a further rise. The arterioles of the kidney are constricted.

SUPRARENAL CAPSULES.

Structure.—On the surface is a fibrous sheath with prolongations into the gland. The glandular portion consists of two parts, the cortex and medulla. The cortex consists of three distinct portions: the outer part, known as the zona glomerulosa, in which the cells are cuboidal in shape, and arranged in clumps; internal to this is the zona fasciculata, in which the cuboidal or spheroidal cells are arranged in longitudinal bundles; internal to this is the zona reticularis, where the cells form a kind of network. The cells of the cortex are polyhedral in shape, and contain globules of fat and lipoids.

Arterioles to the cortex break up in the fibrous prolongations between the columns of cells in the zona fasciculata.

The medullary portion of the gland consists of an irregular meshwork of fibrous tissue, amongst which are large multinucleated cells, and similar cells containing a material which stains faintly brown with chromic acid. There are also non-medullated nerve fibres and nerve cells. In the connective tissue are venous spaces surrounded by plain muscle fibres, which possibly control the circulation from the gland.

Development.—The cortical portion is derived from columns of cells which bud off from the upper part of the Wolffian bodies, and is therefore of mesoblastic origin. This part of the gland corresponds with the single median interrenal body of Balfour, which is present in elasmobranch fishes.

The medullary portion of the gland is developed in connection with the sympathetic nervous system, and is therefore mainly of epiblastic origin. It corresponds with the paired bodies of Balfour, which are segmentally arranged, and are present as such in the elasmobranch fishes.

The Effect of Removal.—It is found that animals die within from twelve to forty-eight hours after removal of their suprarenal capsules. The main symptoms produced in these animals are as follows:—

Progressive muscular weakness with general loss of tone in the vascular system, loss of appetite, and occasional convulsions. Death is due to asphyxia from paralysis of the respiratory muscles. It is found that the blood of animals, dying after the removal of their suprarenal capsules, is toxic for other animals which have been recently deprived of their suprarenal capsules. This blood, however, has no toxic effect upon normal animals.

Experiments on Animals.—If an extract of the *medullary part* of the suprarenal capsule is injected into the veins of a frog, and allowed to circulate, and then an ordinary nerve-muscle preparation is made from the animal and the nerve stimulated by a single induction shock, the muscle twitch obtained has a longer contraction stage and a longer stage of relaxation than a simple muscle curve. This shows that the extract increases skeletal muscle tone. If the extract is injected into the veins of an animal, the arterial blood pressure of which is being recorded, the injection is followed by a distinct rise of arterial blood pressure. If, however, the vagi are cut, or their cardiac ends paralysed by the previous injection of atropine, the rise in blood pressure is found to be greater. If, in the experiment, a limb, the kidney, part of the small intestine, or the spleen is placed in a plethysmograph, it is found that the organ shrinks. This effect can be obtained even if the vaso-motor centre in the medulla is destroyed and the spinal cord paralysed. The effect of the suprarenal extract, therefore, must be a peripheral one, acting on the peripheral neuro-muscular element of the arterioles. It has been shown that, if the blood vessels are under the control of suprarenal extract, and the arterial blood pressure consequently high, the strongest stimulation of the upper cut end of the depressor nerve will not cause the arterial blood pressure to fall (*vide* p. 217).

Oliver and Schäfer found that the extracts from the diseased suprarenal glands of patients, who have died of Addison's disease, do not possess the active principle of the healthy suprarenal gland.

The active principle of the medullary part of the suprarenal capsule is called epinephrin, suprarenin, or adrenalin.

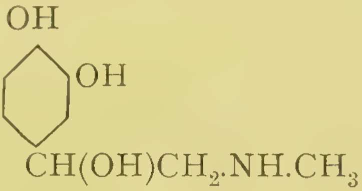
This substance has been demonstrated in the venous blood which leaves the suprarenal bodies. An extremely small dose is sufficient to produce its normal physiological effect. It is believed that, in normal circumstances, small quantities of the internal secretion leave the suprarenal gland in the venous blood, and the epinephrin produces its beneficial effect by acting upon the walls of the blood vessels.

Langley had shown that the effects produced by adrenalin are such as would follow the excitation of the sympathetic nerve which goes to the organ, and it will not act on any structure which is devoid of sympathetic nerves. It is found that adrenalin does not cause vaso-constriction of the pulmonary arterioles; these blood vessels are not supplied by vaso-motor nerves, and for a similar reason adrenalin does not constrict the coronary arteries of the heart or the cerebral arteries. It is concluded, therefore, that the action of adrenalin is upon the vaso-constrictor nerve-endings around the plain muscle of the arterioles.

It is a significant fact, therefore, that the medullary part of the suprarenal capsule is developed in connection with the sympathetic nervous system, and its internal secretion has a stimulating effect upon the nerve terminations of the vaso-constrictor nerve fibres developed in connection with that system. It has been found experimentally that the suprarenal extract, intravenously injected, causes a distinct contraction of the spleen, which is rich in plain muscle and abundantly supplied with sympathetic nerves. Crile has shown experimentally that, in the most profound shock which is associated with vaso-dilatation of the peripheral arterioles, especially those in the splanchnic area, it is possible to keep up the arterial blood pressure and maintain life by the continuous intravenous injection of adrenalin in salt solution 1 in 50,000 to 100,000. The action of the suprarenal extract upon the stomach is to cause inhibition of its muscular movements; at the same time, the sphincter of the pylorus remains contracted. Adrenalin, when subcutaneously injected, or when injected into the peritoneal cavity of an animal, produces glycosuria. It is found that there is a hyperglycæmia, which *may* be due to the epinephrin interfering with the internal secretion of the pancreas. It is thought that adrenalin is formed in the suprarenal capsule from tryptophane (indole amino-propionic acid), which is a chromogen substance derived from protein.

The active principle of the suprarenal capsule is not destroyed by boiling, or by artificial gastric digestion.

Adrenalin has the following formula :—



It has been obtained as a light white crystalline powder, somewhat bitter, sparingly soluble in water; when dissolved in alkalies it is capable of effecting reduction, and it readily absorbs oxygen from the atmosphere.

There is no experimental evidence with regard to the function of the *cortical part* of the suprarenal capsule. It has been suggested that the cortical portion may be connected with the general growth of the body, and its development, puberty, and sexual maturity. It has been found that the cortical part of the suprarenal capsule becomes twice its normal thickness in pregnant rabbits. On the other hand, it has been suggested that the function of the cortical part of the suprarenal capsule may be to produce a substance which neutralises certain poisonous products of nitrogenous metabolism, possibly by aiding their conversion into inert bodies, such as urea; that is, its function is to prevent auto-intoxication.

It is found that the cortex contains large quantities of lipoids, such as cholesterin and lecithin, and the droplets seen in the fresh cells consist of these compounds; and the suggestion that the cortex of the suprarenal capsule plays a part in the metabolism of these substances, appears to be quite a feasible one (Halliburton).

In Addison's disease, in which the suprarenal capsules and the adjacent sympathetic ganglia are found diseased, the patients develop symptoms of general asthenia with a low arterial blood pressure. They also have symptoms of gastro-intestinal irritation, with pigmentation of the skin and mucous membranes; these are symptoms of auto-intoxication. At the same time, these patients derive practically no benefit from the administration of fresh suprarenals or suprarenal extract.

THE PANCREAS.

In the interacinar loose connective tissue of the pancreas are irregular masses of spheroidal cells, known as the cell islets of Langerhans (*vide* p. 109).

These masses of cells are richly supplied with blood vessels. Dale believes that they are formed from the secreting acini of the gland, although it has been suggested that they are developed quite apart from the secreting portion of the pancreas. It is found that, if from a healthy dog the pancreas is completely removed, there is not only no pancreatic juice secreted into the intestines, but the animal develops hyperglycæmia followed by glycosuria. This glycosuria disappears, however, if a fresh piece of pancreas is successfully engrafted into the peritoneal cavity of the depancreatised dog.

It may be concluded that the pancreas, possibly through the cell islets of Langerhans, produces an internal secretion, which may have a particular function in influencing carbohydrate metabolism, as it takes place in two main regions of the body, namely, in the liver and in the tissues generally.

1. **In the Liver.**—The internal secretion of the pancreas is carried to the liver in the portal blood, and there it activates the liver cells in the taking up of the small molecules of glucose. The liver cells, then, by the agency of their endocellular enzyme, build up and retain the larger molecule glycogen. When carbohydrate is required by the tissues, the endocellular enzyme of the liver cells acts in a reverse direction, and gradually converts the glycogen into dextrose, which then leaves the liver in the blood of the hepatic vein.

2. **In the Tissues.**—Some of the internal secretion of the pancreas no doubt leaves the liver and accompanies the dextrose to the tissues. Here it may be that the internal secretion acts as an amboceptor, linking on the dextrose of the plasma to the tissue proteins, especially those in muscle and in the cells of the body. In other words, the internal secretion of the pancreas seems to stimulate the tissue proteins to *adsorb* dextrose, *i.e.* the internal secretion aids constructive carbohydrate metabolism or carbohydrate assimilation in the tissues. It may be, too, that from the excess of dextrose adsorbed to the tissue proteins, the tissues are able to build up the heavier molecule glycogen ; for where carbohydrate

katabolism goes on most actively, there glycogen is stored. Cardiac muscle is especially rich in glycogen.

If the internal secretion of the pancreas is absent, such as occurs after complete removal of the pancreas and in some diseases of the pancreas, the liver appears no longer to be able to store up glycogen. The absorbed glucose is carried in excess to the tissues, which also can no longer assimilate it. The result is that the amount of glucose in the plasma of the blood rises above 0·2 per cent. (hyperglycæmia). The small molecules of glucose are then excreted by the flattened epithelial cells lining Bowman's capsules of the kidney, and sugar is consequently present in the urine (glycosuria). If, however, the excision of the pancreas is incomplete, glycosuria does not follow, showing that a small amount only of the internal secretion of the pancreas is required for carbohydrate metabolism to be normally carried on. Some forms of diabetes mellitus are due to general disease of the pancreas, which involves particularly the interstitial tissue, and hence the cell islets of Langerhans. Opie concludes that more than half of the cases of diabetes mellitus are due to disease of the pancreas, and especially to disease of the cell islets of Langerhans as a result of interacinar chronic inflammation (chronic interstitial pancreatitis).

THE TESTIS.

The loss of the testes by disease, or removal, is followed by well-marked alterations in the body and in its functions. As a rule, there are increase in weight, loss of energy, and impaired vitality. Shattock and Seligmann have demonstrated that the occlusion of the vasa deferentia of young sheep and fowls does not inhibit the free acquisition of secondary sexual characters. They have also shown that, as part result of their operations of caponisation, portions of the testicle were left behind but displaced from their usual position. These portions, severed from their normal nervous connections, grew in their new position, but were devoid of any channels opening externally, and therefore virtually became examples of ductless glands. The fowls, in which this incomplete removal of the testes was practised, developed male characters. The metabolic results, arising from the activity of the grafts of testicular tissue must be attributed to the elaboration of an internal secretion and its absorption into the general circulation (Batty Shaw). Testicular extract is rich in phosphorus bodies, such as the lipoid lecithin.

In the loose connective tissue between the seminiferous tubules are groups of "interstitial cells"; they are polyhedral in shape, and contain yellowish fatty granules; they are somewhat like the polyhedral cells in the cortex of the suprarenal capsule. It is possible that these "interstitial cells" produce the internal secretion of the testis, which exerts such an important influence upon the growth, the mental condition, and the general appearance of the animal (*vide* p. 717).

THE OVARY.

In cases in which the ovaries are ill-developed, or have become atrophied, as occurs at the menopause, or have been removed by previous operation, certain of the symptoms of the menopause arise as follows: General obesity and change in figure, loss of tone of the breasts, frequent headaches, flushings of the skin, tremors, pseudo-anginal attacks, pain over the heart region, and certain psychoses. Some of these symptoms disappear on the administration of ovarian extract. In the stroma of the ovary there are cells which resemble the "interstitial cells" of the testis. These stroma cells are polyhedral in shape; they lie close alongside the blood vessels which traverse the stroma of the ovary, and have the general appearance of the polyhedral cells present in the cortical portion of the suprarenal capsule. It is interesting to note that the suprarenal capsules, the testes, and the ovaries are all developed in connection with the Wolffian bodies.

It has been suggested that the internal secretion of the ovary is derived from these stroma cells, and that its function is to dominate menstruation. It has also some function in influencing the metabolic changes which occur in the breasts, and therefore in helping to maintain female characteristics (*vide* p. 720).

THE DUODENAL MUCOUS MEMBRANE.

The mucous membrane of the duodenum and that of the upper part of the jejunum produce an inactive substance called *pro-secretin*. This is normally extracted by the sodium chloride which is in solution in the acid gastric chyme. After its extraction, the "pro-secretin" is acted upon by the free hydrochloric acid, which is also present in the acid gastric chyme. The effect of the action of the hydrochloric acid is that an active substance called *secretin* is split off from the *pro-secretin*; the secretin thus liberated appears to be absorbed by the mucous membrane of the duodenum and the jejunum, and is taken by the blood stream or the lymph stream to the pancreas, where it stimulates the acinar cells to pour out their secretion. The secretin is also taken by the blood to the liver, where it stimulates the liver cells to increased activity, and therefore to produce bile. At the same time that secretin is liberated, there is another substance produced, which lowers arterial blood pressure by causing vaso-dilatation in the splanchnic area, one of the purposes of which, presumably, is to increase the arterial blood supply of the pancreas, and also possibly of the liver, whereby the activity of these organs is further increased (*vide* p. 109).

THE PYLORIC GLANDS OF THE STOMACH.

Edkins found that an extract of the mucous membrane from the pyloric end of the stomach, when injected into the blood of a fasting animal, caused a copious secretion of active gastric juice.

The pyloric glands therefore appear to produce a hormone, which is called *gastric secretin* or *gastrin*, the function of which is to stimulate the fundus glands of the stomach to pour out gastric juice (*vide* p. 99).

CHAPTER XXII.

THE TISSUE-FLUIDS: LYMPH AND CEREBRO-SPINAL FLUID.

The chief fluid in the body is the blood, which in some regions comes into *direct* contact with the tissues. This takes place in the spleen and other hæmo-lymph glands, in the red marrow of bone, and in the placenta. Generally, however, the blood gives rise to a tissue fluid which is found in the interstitial spaces between the connective-tissue cells, which are present between the blood vessels and the tissues of the body. The aqueous humour produced by the ciliary processes, the cerebro-spinal fluid produced by the choroid plexuses, and the fluid produced in the peritoneal, pleural, and pericardial cavities; that also formed in the tunica vaginalis, in the synovial cavities and synovial sheaths of the tendons, may be considered as tissue fluids. The greater part of the tissue fluid passes from the interstitial spaces into the overflow vessels, which are the lymphatics; these eventually pour their contents into the venous system.

LYMPH.

This is the fluid which is found in the lymphatic vessels, in the thoracic duct, and in the large lymphatic trunks; it varies in composition in the different parts of the body. Lymph flows in the lymphatic vessels which accompany the veins, traverses the lymphatic glands, and makes its way through the thoracic duct and right lymphatic duct into the innominate veins at the root of the neck.

The Origin of Tissue Fluid.

Tissue fluid is found in the interstitial spaces in the body, whence it is supplied to the tissues; in fact, it is usually stated that it "bathes the tissues." It is practically impossible to determine its composition, but it derives its constituents, such as water, protein, fat, carbohydrate, and salts from the blood, and supplies them to the tissues, where active metabolic changes occur. It receives back from the tissues some of the waste products of katabolism, such as CO_2. Some of these waste products return from the tissues in the lymph which flows in the lymphatics, and some are absorbed by the capillaries, through which they return to the veins. It is because of the greater molecular concentration of these waste products in the tissue fluid that they diffuse into the blood plasma.

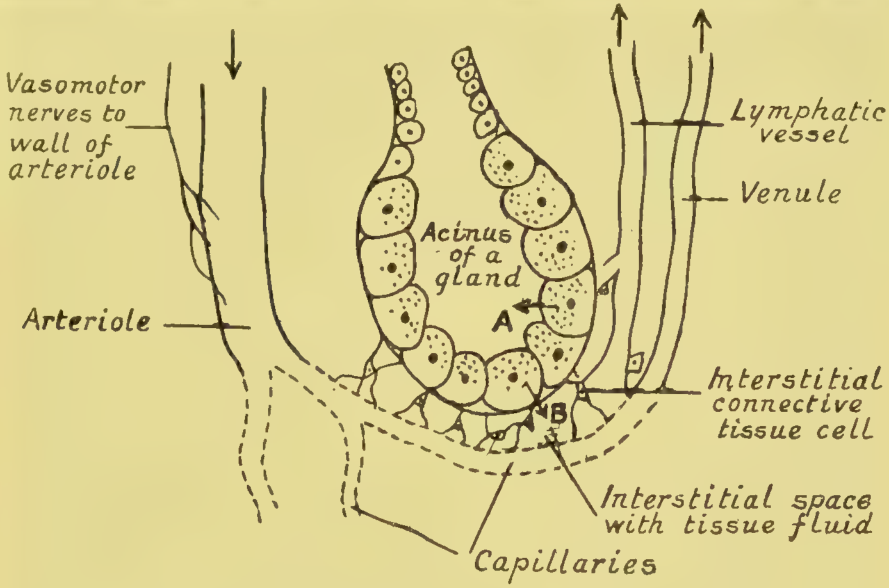

Vasomotor nerves to wall of arteriole
Arteriole
Acinus of a gland
A
B
Lymphatic vessel
Venule
Interstitial connective tissue cell
Interstitial space with tissue fluid
Capillaries

FIG. 38.—Diagram to represent the relationship of the tissue fluid to the capillaries and to the tissues.

A. Products of cell activity pass into the acinus of the gland.
B. Waste products pass back into the tissue fluid.

The tissue fluid is derived from the capillaries, but *how* this is exactly brought about is an open question. The blood plasma contained in the capillaries is separated from the fluid in the interstitial spaces by an endothelium, and the tissue fluid has to pass through this thin wall. It is possible that it passes through partly by a process of *transudation*, which depends upon the permeability of the capillary walls, and is a physical process including filtration, osmosis, and dialysis, and possibly partly as the result of *secretion*, which is a physiological process depending upon the specific action of the endothelial cells lining the capillaries. It is quite possible, however, that both these physical and physiological processes occur during the production of tissue fluid.

By *filtration* is meant the passage of water and substances dissolved in the water through a membrane due to an excess of hydrostatic pressure on one side of the membrane over that on the other. This difference of pressure constitutes the *filtering force.* Now, it is generally maintained that the capillary blood pressure is greater than that of the fluid in the connective tissues; if this is so, it is possible that the difference of hydrostatic pressure is one factor in the formation of tissue fluid, provided that the capillary wall allows the fluid to permeate it. On the other hand, Leonard Hill holds the view that such a thing as a filtration pressure is impossible in the living body. He states that "in the case of a limb enclosed in the skin, or of a kidney enclosed in its capsule, the whole semi fluid mass must be at capillary pressure. The whole of the body fluids, unless influenced by gravity or the localised compressive action of muscles, or the secretory activity of the cells, are at the same pressure, namely, that of the capillaries." Now the products of tissue activity—for example, the products of the cubical cells lining the acinus of a gland—pass into the gland lumen, but the waste products pass back to the tissue fluid (*vide* Fig. 38); and it has been shown by Bayliss and Starling that some of the products of tissue katabolism (not sarcolactic acid or CO_2) exert a specific local vaso-dilator action upon the neighbouring arterioles. If this is so, such arteriole dilatation must of necessity cause an increased volume of blood in the capillaries supplied by the arteriole, and consequently a rise of capillary blood pressure. It is found too, as a rule, that active vaso-dilatation, caused by stimulation of vaso-dilator nerves, causes an increased lymph flow from the part. In these circumstances, there will be a filtration from the capillaries into the interstitial tissue spaces.

By *osmosis* (diffusion of water) is meant the passage of water molecules through an animal membrane. Salts in solution exert a certain osmotic pressure, *i.e.* attract water molecules, and it is possible in this way that salts, or their equivalents in solution in the tissue fluids, attract the water molecules from the plasma in the blood capillaries. Now Asher has shown that increased tissue activity is associated with an increased lymph flow from the part, which must to a certain extent be due to increased production of tissue fluid. Increased tissue activity is associated with the liberation of lighter molecules from heavier ones, and it is possible that these lighter molecules liberated from the cells, whence the metabolic processes proceed, pass into solution in the tissue fluid, and there exert an osmotic pressure which results in the attraction of more water from the capillaries into the interstitial spaces outside; hence there follows an increase of the tissue fluid. Leathes has found that during tissue katabolism the osmotic pressure of lymph is greater than that of the blood. Asher maintained that lymph is a product of the activity of tissue cells, and independent of capillary blood pressure. He found that the activity of the salivary glands, produced reflexly from the mouth, causes an increased flow of lymph along the lymphatic vessel in the neck; but that, if the animal is previously atropinised, the glandular activity consequently being prevented, stimulation of the peripheral end of the cut chorda tympani nerve caused vaso-dilatation, though *no* increased lymph flow followed, for there was no glandular activity. Bainbridge has shown that the increased secretion of pancreatic juice, produced by the injection of *secretin*, is accompanied by an increased flow of lymph in the thoracic duct; but it must be remembered that secretin causes vaso-dilatation of the vessels of the pancreas and of the liver. Increased tissue activity is no doubt associated with an increased production of tissue fluid, but there are other factors which must be considered.

Starling is of opinion that proteins in solution exert an osmotic pressure, though others suggest that it is the ions of the inorganic salts, in solution with the proteins, and which are adsorbed (an intermediate state between mechanical mixture and chemical combination) to the proteins, which really exert the osmotic pressure.

By *dialysis* is meant the passage of substances in solution through an intervening membrane (diffusion of substances in solution), the fluid on either side of the membrane being under the same hydrostatic pressure. Substances which pass through such membranes are called crystalloids, and include the inorganic salts. Substances which have heavy molecules, such as serum albumin and serum globulin, will not pass through dead animal membranes; these substances are called colloids. It may be concluded, then, that the salts and dextrose of blood plasma dialyse through the capillary walls into the interstitial spaces outside, even assuming that the cells lining the capillary walls remain passive. It is generally accepted that the processes of osmosis and dialysis are more important in tissue fluid formation than that of filtration.

Proteins, such as serum albumin and serum globulin, are found in lymph; it may therefore be concluded that they exist in the tissue fluid, and are thence derived from the blood plasma. How, then, do these proteins get into the tissue fluid? They are colloids, and do not dialyse. It must be assumed, therefore, that the endothelial cells lining the capillaries do *not* behave like the dead membrane of a dialyser, but have a selective or secretory (physiological) action, picking out some serum albumin and serum globulin, and passing them through into the tissue fluid in the interstitial spaces outside the capillaries.

Ludwig held the mechanical view of lymph formation, *i.e.* that there are two factors at work, *filtration* and *diffusion* (osmosis and dialysis).

Heidenhain suggested that lymph is secreted by the endothelial cells lining the blood capillaries.

Asher holds the view that tissue activity is the cause of lymph formation, and consequently of lymph flow.

Halliburton says: "Lymph formation is doubtless mainly influenced by the physical conditions present, for the action of such thin cells as those of the capillary wall cannot be sufficiently great to entirely counteract these conditions; at the same time, it is impossible to deny that there is some such action, as may be described by the terms 'selective' or 'secretory.'"

Lymph, as it occurs in the lymphatic vessels, varies in composition according to the part of the body from which it is obtained. That from a limb contains many of the constituents of blood plasma, which gives rise to the tissue fluid, and also some of the waste products derived from the tissues themselves. Some of the waste products of the tissues, however, which are delivered to the tissue fluid, leave that fluid and pass back into the capillaries, and are thus carried to the heart by the blood stream. That absorption does take place by the blood capillaries has been proved by Starling and Tubby. They injected a solution of methylene-blue into the serous cavities of an animal, and found that it appeared in the urine within five minutes, whereas the methylene-blue did not appear in the thoracic duct for at least half an hour.

Lymph obtained from the thoracic duct is derived from the limbs, from the lacteals, which contain the chyle, the molecular basis of which is fat, and from the liver. Lymph may be obtained by inserting a cannula into the thoracic duct.

Properties of Thoracic Duct Lymph.—It is an alkaline fluid, sp. gr. 1015. When removed from the thoracic duct it clots, the thrombin or thrombase present acts upon the fibrinogen, causing the production of insoluble fibrin. Lymph contains lymphocytes derived from the lymphatic glands, which it traverses.

COMPOSITION OF LYMPH.

Water	94 per cent.
Solids	6 ,,
Proteins { fibrinogen . serum globulin serum albumin } .	3 ,,

Fat, in fine emulsion.
Carbohydrate—dextrose.
Salts—NaCl, $NaHCO_3$, Na_2CO_3, Na_2HPO_4, $CaCl_2$.
Extractives—*e.g.* urea.
CO_2 in solution.

Lymph from a limb contains 2 to 3 per cent. of protein, that from the intestines 4 to 6 per cent., and that from the liver 6 to 8 per cent. Starling associates these differences of protein percentages with the different permeabilities of the capillary walls for protein; others, however, explain these differences by stating that they are due to varying amounts of protein taken up by the tissues from the tissue fluid.

Relation of the Lymphatic Vessels to the Lymphatic Glands.—The afferent lymphatic vessel enters the convex aspect of a lymphatic gland by two or three openings. These afferent vessels traverse the plain muscle in the wall of the gland, and pour their contents into the spaces in the retiform tissue between the trabeculæ of the cortex of the gland. The efferent lymphatics commence by three or four tributaries, which arise in the medulla of the gland, the cells in the retiform tissue here being continuous with the endothelial cells which line the efferent lymphatic vessels. The tributaries leave the hilum of the gland, and converge to form the efferent lymphatic vessel. The lymphocytes enter the lymphatic vessels at the medullary portion of the lymphatic glands.

Measurement of Lymph Flow.—This may be done by placing a cannula into the thoracic duct, when the amount of lymph so obtained represents that coming from the limbs, liver, and intestines. The amount flowing from the limbs may be disregarded if the animal is kept at rest, for very little lymph (if any) flows from a limb kept quite still. If it is required to measure the lymph flow from the intestines only, the liver may be excluded by previous ligature of the lymphatics, which return from the liver to the thoracic duct. These leave at the portal fissure. If the thoracic aorta is obstructed, the capillary blood pressure becomes lowered, and the lymph flow from the intestines is consequently decreased. If the aortic obstruction is removed, the capillary blood pressure rises, and lymph once more flows along the thoracic duct. Ligature of the portal vein at the transverse fissure of the liver causes a marked rise in the blood pressure in the capillaries of the intestines, and a greatly increased flow of lymph from the thoracic duct; in these circumstances, the lymph contains less protein than normal.

It has been stated that the formation of tissue fluid, and consequently lymph, depends upon the permeability of the capillary walls. Now, in the liver the capillary walls are the thinnest possible, and are probably replaced by liver cells at the sinusoids. At any rate, it is possible that the blood plasma here comes into direct contact with the liver cells. The permeability is consequently greatest in the liver. If the inferior vena cava is obstructed above the openings of the hepatic veins, the pressure in the intralobular capillaries is considerably raised, and consequently the pressure in the lobular blood capillaries and sinusoids is raised too, leading to a large outflow of fluid and protein in solution into the liver lymphatics. In these circumstances, there is a large flow of lymph, which is particularly rich in protein, from the thoracic duct. If, however, the liver lymphatics are ligatured in this experiment there is no increased flow along the thoracic duct.

Lymphagogues are substances which cause an increased flow of lymph from the thoracic duct. Heidenhain divided them into two classes, one class (Heidenhain's second class of lymphagogues) containing such substances as dextrose, sodium chloride, urea; and the other class containing substances such as extract of crayfish, of mussels, leech extract, and solution of commercial peptone (toxins and strawberry extract may be added) (Heidenhain's first class of lymphagogues). The substances, such as dextrose and sodium chloride, if injected into the blood, cause a rise of its osmotic pressure, the consequence of which is that water is drawn into the capillaries from the interstitial spaces; there is then, for the time being, hydræmic plethora. This raises the blood pressure in the capillaries, veins, and arteries; the result of this is that there is an increased transudation of fluid from the capillaries into the connective-tissue spaces in consequence of the raised capillary pressure, consequently there is an increased flow of lymph. On the other hand, it is possible that salts introduced into the blood dialyse out into the interstitial spaces and there excite tissue activity, which causes a disintegration of large complex unstable molecules into a number of small and more stable molecules. The total output of an animal cell has a higher osmotic pressure than the total income, so that all the metabolic processes in the tissues tend to increase the osmotic pressure of the lymph (Starling). The increased osmotic pressure of the tissue fluid causes water to flow from the capillaries into the interstitial spaces, and there is therefore an increased formation of tissue fluid and consequently an increased lymph flow.

The lymphagogues, including commercial peptone, leech, and crayfish extracts, act probably in a totally different way from the other class. Heidenhain believed that these bodies excited the secretory activity of the endothelial cells of the capillaries, whereas Starling states that they increase the permeability of the capillary walls by injuring the vitality of the endothelial lining, and in so doing allow an increased amount of fluid to leave the capillaries and to accumulate in the interstitial spaces. These substances seem to act chiefly upon the lobular blood capillaries in the liver. According to Kusmine, these substances cause acute degeneration of the liver cells; that is, they act as liver cell poisons, and it is therefore possible that they may cause an increase in lymph flow in two ways: (1) By producing a pathological katabolism of the cell protoplasm, whereby the osmotic pressure of the tissue fluid is greatly increased, and more water is consequently drawn into the interstitial spaces; (2) by injuring the capillary walls.

The liver capillaries are not the only ones influenced by these lymphagogues. Those in the intestinal wall and skin are also affected. Urticaria, or nettle-rash, is a local œdema due to an increased permeability of the capillary walls due to the poisoning of the endothelial cells by shell-fish extracts, and the vesication, or blistering, which follows burns is probably due to local injury of the endothelial cells, followed by an increased permeability. After the injection of curare, although the capillary blood pressure falls, there is an increased lymph flow, and that which comes from a limb, in these altered circumstances, is as rich in protein as that which comes from the liver under normal conditions, suggesting, therefore, that curare poisons the endothelium, and increases the permeability of the capillary walls.

Movements of Lymph.—Lymph flows from the peripheral portions of the body towards the innominate veins, and there are various factors which cause this onward movement.

Pressure Differences.—It has been already stated that the capillary blood pressure is probably greater than that in the tissue spaces, which may account for a flow of fluid from the capillaries, but the pressure in the large veins varies from 0 mm. Hg to -4 mm. Hg. During inspiration the intrathoracic pressure is reduced to as much as -30 mm. Hg, and that of the abdomen increased through descent of the diaphragm. This is an additional factor in inducing lymph to flow from the abdomen towards the thorax. Just as the aspiratory effect of inspiration is to draw blood into the thorax, so it also induces lymph to flow into the thorax, and hence into the veins.

Lymph Hearts.—In the frog and toad there are two pairs of lymph hearts, the walls of which contain plain muscle and contract rhythmically. The anterior pair of lymph hearts lie behind the transverse processes of the third vertebra and beneath the shoulder girdle; they are innervated through the third segment of the cord, and open into the subscapular veins. The posterior pair of lymph hearts lie along the sides of the urostyle; they are innervated by the eighth segment of the cord, and communicate with the femoral veins.

From the Limbs.—From a resting limb there is practically no flow of lymph, but muscular movements produce an increase of pressure upon the interstitial lymph spaces and the lymphatic vessels, and in this way cause an onward flow. Return is prevented by the valves which are present in the larger lymphatic vessels. The effect of massage properly applied to a part is to cause an increased lymph return, and to remove the products of metabolism from that part.

From the Head and Neck.—Lymph return is brought about by the effect of gravity and muscular movements.

From the Intestines.—The lymph return is caused by the peristaltic movements of the intestinal wall, by the contraction of the plain muscle which is situated in the villi around the lacteal radicals, by the compression of the viscera caused by the descent of the diaphragm during inspiration, and by the presence of valves in the lymphatic vessels, which prevent a backward flow.

CEREBRO-SPINAL FLUID.

This fluid plays the part of the tissue fluid of the central nervous system. It is present in the ventricles of the brain and central canal of the spinal cord. It is also present in the subarachnoid space surrounding the brain and cord; there is a great deal more of it about the base of the brain than over its dorsal aspect. The subarachnoid space—that is, the space between the arachnoid mater and the pia mater—communicates by the foramen of Majendie, an opening in the epithelial and pial roof of the ventricle, with the cavity of the fourth ventricle. In this way the cavities of the brain and spinal cord communicate with the subarachnoid space. The cerebro-spinal fluid is, in all probability, produced partly as a transudation from the capillaries of the choroid plexuses, partly as a secretion by the epithelial cells over the plexuses, and partly as the tissue fluid which surrounds the pial capillaries in the grey matter of the brain; this is contained in the perivascular spaces.

Cerebro-spinal fluid is colourless and alkaline, having a specific gravity of between 1006 and 1008.

Composition of Cerebro-spinal Fluid.—

WATER.—Mostly.

SOLIDS.—Protein (trace), chiefly globulin; if the membranes of the brain or cord are inflamed, there is much more protein present.
Carbohydrate; dextrose, which may be demonstrated by the phenyl-hydrazine test.
Salts, as in blood plasma.
Occasionally a few leucocytes.

In normal circumstances, cerebro-spinal fluid contains no choline, but in organic disease of the central nervous system the products of nerve degeneration pass into the cerebro-spinal fluid and may be detected there. Under these conditions the presence of nucleo-protein and choline may be demonstrated (*vide* p. 53). In inflammation of the membranes of the brain and cord some lymphocytes and many more leucocytes may be present in the cerebro-spinal fluid.

The pressure of the cerebro-spinal fluid may be measured in an animal by inserting a cannula through the lamina of the axis. Leonard Hill states that the brain pressure, the cerebral venous pressure, and the cerebro-spinal fluid pressure are one and the same. Cerebro-spinal fluid may be removed from the spinal meninges for chemical and microscopical examination by Quincke's lumbar puncture. The needle by which the fluid is to be withdrawn is inserted between the third and fourth lumbar vertebræ on the right side, the patient usually lying upon his left side with his knees drawn up during the operation.

SECTION VI.

THE NASAL CAVITIES, NASO-PHARYNX AND LARYNX.

CHAPTER XXIII.

THE NASAL CAVITIES.

THE functions of these cavities may be said to be primarily, **respiratory** and **olfactory**; and secondarily, **vocal.**

A. The respiratory region includes the inferior and middle and part of the superior meatus of the nose. The inferior and middle turbinal masses project into this region from the outer wall, but a narrow interval is left between them and the septum. Practically all the accessory sinuses open into, and discharge their secretions into, this respiratory portion of the nasal cavity.

The special functions of the respiratory region of the nose are—

1. *To Warm the Inspired Air.*—This is effected by its passage over the very vascular turbinal masses; and, however cold inspired air may be, it is always sufficiently warmed by the time it reaches the larynx (*vide* p. 331).

2. *To Moisten the Inspired Air.*—The secretion of the larger glands in the respiratory area, the secretion of the vascular mucous membrane, and the secretion of the various cells and sinuses in the vicinity saturate the air with moisture as it passes through the respiratory region of the nose.

3. *To Remove Injurious Constituents of the Inspired Air.*—The removal of dust, etc., is largely effected in the cutaneous vestibule of the nose. Just inside the nostrils there are strong vibrissæ with out-turned points, moistened by the secretions

of the nose, which form an excellent first line of defence against foreign particles.

Smaller foreign bodies, bacteria, etc., are deposited on the moist surface of the respiratory area, and examination has shown that these rapidly decrease in number on the mucous surface from before backwards.

The respiratory surface, moreover, is ciliated; whereas the olfactory area is not so definitely ciliated, though there are small patches of ciliated cells here and there.

The mucous secretion is not actively bactericidal, at least for most organisms; but experimentally, at any rate, it affords a poor culture medium for micro-organisms.

B. The olfactory area is confined to the upper turbinal mass and part of the upper meatus, the corresponding part of the roof of the nasal cavity, and the upper third or less of the septum nasi. The enclosed area is a narrower space than the lower respiratory region. The terminals of the olfactory nerves, distributed over the olfactory area, are excited by substances reaching them from the air passing through the nasal cavities (*vide* p. 624).

C. The vocal function of the nose and the accessory cavities is that of a complex resonating chamber. The acoustic properties of the nasal cavities and accessory sinuses are readily interfered with when the mucous membrane lining these cavities becomes swollen. This occurs as the result of a catarrh of the nose (*coryza*) or disease of one or both of the maxillary antri.

Under these altered conditions, the quality of the voice becomes affected by interference with the normal production of the over-tones.

Although the respiratory and olfactory regions are usually described separately, and have certain anatomical distinctions, yet it must be borne in mind that they are continuous. The thoracic movements of inspiration lead to a negative pressure in the naso-pharynx; the result of this is that air is withdrawn from all the meatuses that reach the neighbourhood of the posterior nares, and even from the spheno-ethmoidal recess. In this way air is drawn in from the outside into the whole nasal cavity; but probably the greatest passage of air is through the lower and more open respiratory area, though a certain amount must also pass through the upper nasal cavities.

In the process of sniffing, for example, the first moment of contact of the odoriferous substance with the olfactory area is made as strong as possible by closing the mouth and by giving a sudden inspiratory movement. The sudden fall of pressure in the naso-pharynx leads to a sudden removal of the air which is present in the olfactory as well as the respiratory region, and this is rapidly replaced by fresh air drawn in from without.

Any condition which cuts off the front and lower part of the olfactory region from the general nasal cavity converts it into a sinus like the other accessory sinuses, which do not completely empty themselves with the fall of intranasal pressure which occurs during inspiration, provided the mouth is kept closed. In this way the advent of odoriferous substances does not take place, and the sense of smell appears to be lost.

The accessory sinuses act as resonating chambers for the voice, and lessen the "damping" of the walls of the cavity to vibration. They also produce secretions, but probably they have little to do with the other functions of the nose. The antrum of Highmore enables the upper jaw to reach a large size without much increase in weight, and a corresponding result is obtained by the frontal and sphenoidal sinuses, and in all probability this fact explains their presence. It is quite possible, therefore, that their acoustic properties are quite incidental.

THE NASO-PHARYNX.

This region has a respiratory and a vocal function. It serves as a resonating chamber, acting, with the other cavities which lie between the vocal cords and the exterior, in forming and intensifying the over-tones or harmonics of the produced laryngeal sound, and thus has a large share in the determination of the *timbre* or quality of the voice.

The position of the soft palate and the size of the opening into the naso-pharynx vary with the different sounds produced; generally speaking, however, it may be said that the soft palate is raised during the production of high notes, and depressed during the production of low notes.

No particular function can be assigned to the lateral recess. The pharyngeal orifice of the Eustachian tube is opened during the act of swallowing at the time of the raising of the soft palate.

The part played by the palate during deglutition is considered under that heading (*vide* p. 146).

THE LARYNX.

The larynx is that part of the respiratory tract, connecting the pharynx with the trachea, which is specialised as the organ of the voice. It is patent in ordinary circumstances, affording passage to the air of respiration, and closed only during the act of swallowing and violent expiratory efforts, such as coughing.

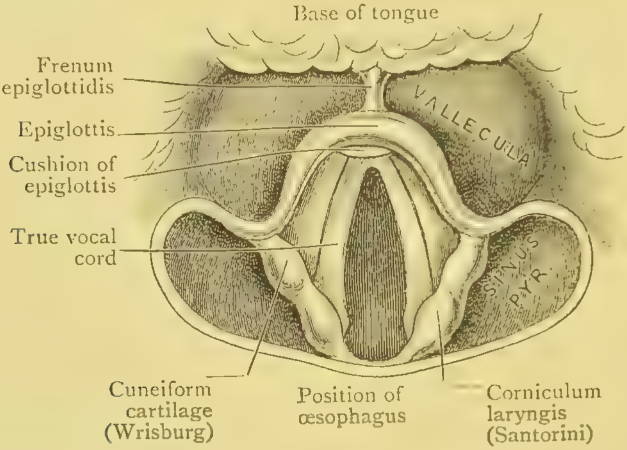


FIG. 39.—The larynx, as seen in the living person by means of the laryngoscope. (Cunningham.)

The cavity of the larynx is divided into three parts—upper, intermediate, and lower—by the prominent superior and inferior laryngeal cords.

The **inferior, or true, vocal cords** produce the rapidly changing air waves which constitute audible sounds. The differences in tension of these cords cause variation in the pitch of the fundamental note of the sound.

The **superior, or false, vocal cords** seem to be connected developmentally with the remains of the framework of the aditus laryngis, but that they serve some function seems to be suggested by their persistence in size, though the nature of this function is not understood. Presumably they have something to do with voice production, because, in the production of high notes they are brought near each other, though they do not vibrate in the production of low tones, but are held widely apart.

The **ventricle and saccules** of the larynx may be regarded as resonating and intensifying chambers, situated just over the vibrating cords, and lessening, by their pressure, the "damping" of the vibrations that may occur in such a small cavity.

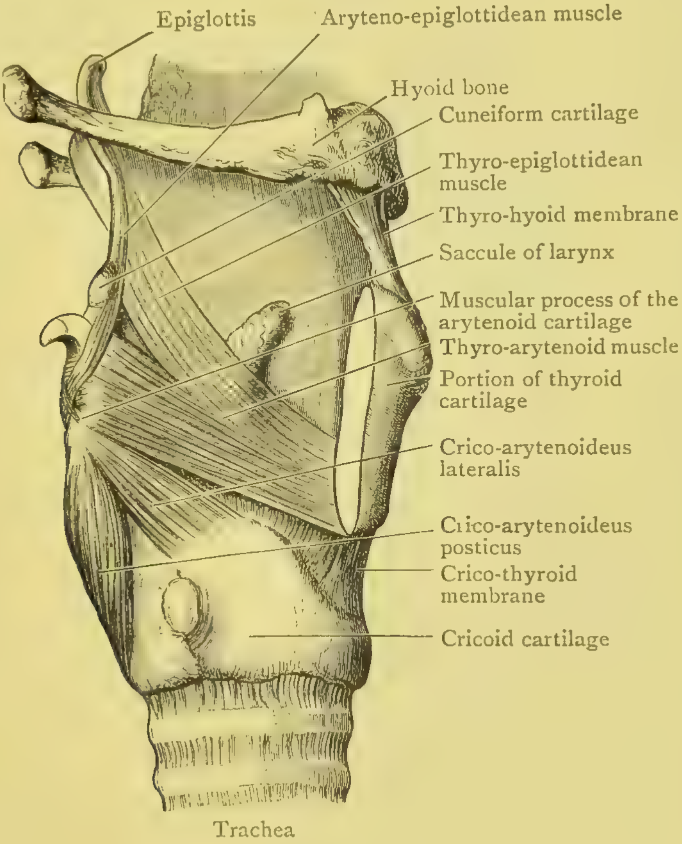

Epiglottis
Aryteno-epiglottidean muscle
Hyoid bone
Cuneiform cartilage
Thyro-epiglottidean muscle
Thyro-hyoid membrane
Saccule of larynx
Muscular process of the arytenoid cartilage
Thyro-arytenoid muscle
Portion of thyroid cartilage
Crico-arytenoideus lateralis
Crico-arytenoideus posticus
Crico-thyroid membrane
Cricoid cartilage
Trachea

FIG. 40.—Muscles in the lateral wall of larynx. (Cunningham.)

The **epiglottis** should be regarded as somewhat rudimentary in the human subject. It does not close down over and shut off the larynx during the act of swallowing, as is sometimes stated, but merely overhangs it. It is conceivable that the epiglottis may prevent fluids from reaching the laryngeal opening when they trickle over the back of the tongue *without the act of* swallowing, and that it directs them, aided by the aryteno-epiglottidean folds, into the pyriform fossa, and consequently into the lower part of the pharynx.

The **movements of the larynx** may be considered under two headings,—those concerned with the production of voice, and those that have to do with the act of swallowing.

1. Laryngeal Movements concerned with Voice Production.

The production of the tone and the intensity of the voice depend upon the state of tension of the true vocal cords, and the amount of freedom allowed to the passage of air between them. The muscles which act on the cords are primarily concerned in this function.

(*a*) *Decreased tension* is brought about by approximating the points of attachment of the cords by contraction of the arytenoid muscles. When the cords are already stretched, the elastic return to the state of rest lessens the tension of the true vocal cords without muscular contraction.

(*b*) *Increased tension* is brought about by separating the points of attachment of the vocal cords; this is effected by the crico-thyroid muscles, acting from the cricoid cartilage, tilting the thyroid cartilage forward and away from the arytenoid cartilages. The lower fibres of the muscle also have a more directly forward pull upon the lower cornua of the thyroid cartilages. Some observers, however, consider it more likely that the muscles act from the thyroid cartilage, tilting up the cricoid cartilage, and thus pushing back the arytenoid cartilages; but the former view is more generally accepted.

(*c*) *Abduction and Adduction of the True Vocal Cords.*—The former usually occurs with relaxation, and the latter with increased tension. These changes in position of the cords are produced by movements of the arytenoid cartilages at their articulations with the cricoid cartilage. Abduction is produced by the posterior crico-arytenoid muscles pulling back the muscular processes of the arytenoid cartilages, so that the vocal processes swing outwards; the opposite effect, adduction, is produced by the lateral crico-arytenoid muscles pulling the muscular processes of the arytenoid cartilages forward.

The arytenoideus muscle, acting alone, approximates the two arytenoid masses, and closes the posterior ("respiratory") area of the glottis.

Some of the innermost fibres of the thyro-arytenoid muscles are attached to the cords for some little distance, and are sometimes described separately as the "ary-vocales" muscles. Their function is not understood. It has been held that they shorten the vibrating segment of the vocal cords considerably, and are thus probably concerned in the production of the falsetto voice.

The movements just considered are not quite so simple in their nature as might be supposed from the account given. The muscles mentioned have not, in most cases at any rate, a direct pull in the plane of the vocal cords, but have an oblique action. The opposing muscles, which act simultaneously here as elsewhere in the body, are those which counteract all the directions of the pull. Thus, in abduction of the vocal cords, the posterior crico-arytenoid muscle not only rotates the arytenoid cartilage outwards by pulling on its muscular angle, but it also tends to depress it; in fact, it tends to pull the whole arytenoid downwards, backwards, and inwards. This calls into play the steadying action of the lateral crico-arytenoid and the thyro-arytenoid muscles.

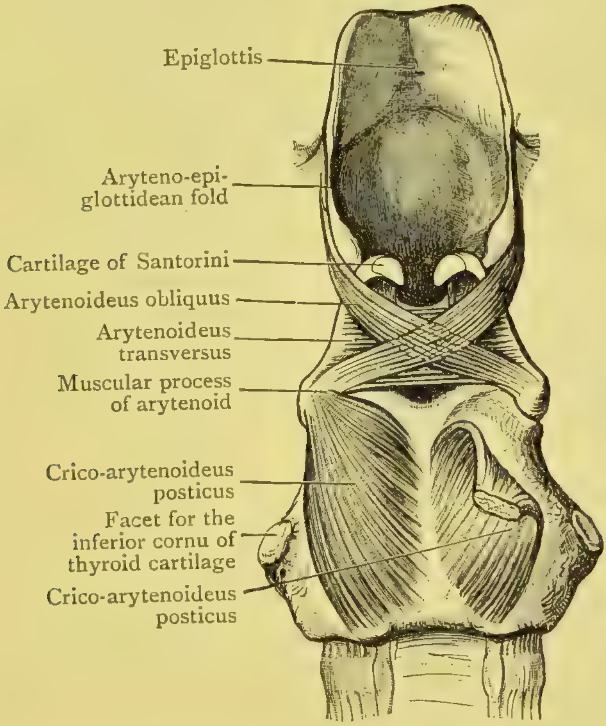

Epiglottis
Aryteno-epi-glottidean fold
Cartilage of Santorini
Arytenoideus obliquus
Arytenoideus transversus
Muscular process of arytenoid
Crico-arytenoideus posticus
Facet for the inferior cornu of thyroid cartilage
Crico-arytenoideus posticus

FIG. 41.—Muscles on the posterior aspect of the larynx. (Cunningham.)

In a similar manner, when the crico-thyroid muscles contract in order to increase the tension of the vocal cords, the arytenoid masses would be pulled forward, if they were not more or less fixed in their position by the arytenoid muscle holding them together, the posterior crico-arytenoid muscle holding back the mass thus formed.

This fixation of the arytenoid masses must also take place when the vocal cords are relaxed by the thyro-arytenoid muscles, but probably under these conditions the arytenoid is not so strongly contracted, and the posterior crico-arytenoid muscles tend to produce an effect of abduction.

In adduction, the tendency for the lateral crico-arytenoid muscles to pull the arytenoid cartilages outwards and forwards is counteracted by the arytenoideus and posterior crico-arytenoid muscles, and by the upper fibres of the thyro-arytenoid muscles; with this must also be some fixation of the thyroid cartilage by the crico-thyroid muscles.

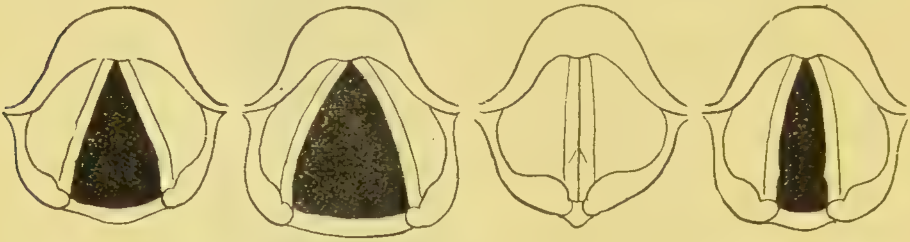

Quiet respiration. Deep inspiration. Phonation. Cadaveric Position.

FIG. 42.—The various positions of the vocal cords. (Harold Barwell.)

The state of increased tension of the vocal cords is usually combined with adduction, and greater resistance to the passage of air between the cords; abduction and lowered tension, as a rule, occur together.

The pressure of air in the trachea varies directly with the height of the note produced, a very high note giving a pressure considerably more than ten times that present when a very low note is produced.

Partly as a result of the increased tracheal pressure, and partly from muscular contraction, the larynx, as a whole, is elevated when a high note is sounded; the uvula and soft palate are also raised. The muscles which raise the larynx are those which act from higher fixed points; that is, the mylo-hyoids and the thyro-hyoids, and also the stylo-pharyngei and the palato-pharyngei.

The production of a high note implies muscular effort, and this effort in the larynx, which affects the general constricting muscle mass, is shown by the tendency of the false vocal cords to move towards the middle line. This movement is no doubt due to the contraction of the upper fibres of the thyro-arytenoid muscles, and the movement backwards of the epiglottis is probably due to the same cause; for the upper fibres of these muscles form the thyro-ary-epiglottidean group of fibres.

The **nerve supply** of these intrinsic laryngeal muscles comes from the recurrent laryngeal nerve, except that of the crico-thyroid, which is innervated by the external laryngeal branch of the superior laryngeal nerve.

Paralysis of the crico-thyroid muscle, directly limiting the power of increasing the tension of the vocal cords, and interfering with the proper use of other muscles in their actions, renders the voice harsh and deeper.

Lesions affecting the recurrent laryngeal nerve have an effect on all the remaining intrinsic laryngeal muscles, but experiment confirms what is found after death, and also in disease, that the branch to the posterior crico-arytenoid muscle is the first to lose its functional power, leading to loss of the abducting power on the side affected. This results in a more mesial position of the vocal cord, together with laryngeal dyspnœa, particularly on exertion; but the voice may remain unaffected or, at any rate, very nearly so.

Paralysis of the arytenoideus results in separation of the arytenoid masses, with over escape of air between them, and in consequence a feeble and hoarse voice.

Paralysis of the adductor muscles tends to slackness, and a flapping of the vocal cord upon the affected side.

Incomplete unilateral paralysis of the recurrent laryngeal nerve occasionally results in double tones in the voice, owing to unequal tension of the two vocal cords.

2. Laryngeal Movements concerned with Deglutition.

The movements which occur in the larynx during deglutition may be divided into those produced by the intrinsic muscles in order to close the laryngeal opening, and those produced by the extrinsic muscles acting as a whole upon the larynx.

Intrinsic Movement.—The larynx, which in normal circumstances is open, is closed during swallowing by the approximation of the arytenoid masses to each other, and their movement forward into close relation with the epiglottis. The arytenoideus approximates the arytenoid masses, and the thyro-ary-epiglottidei, together with the aryteno-epiglottidei, draw the masses forward against the epiglottis.

As a result of the contraction of these muscles, the laryngeal opening is compressed into a small **T**-shaped slit with closely applied edges. The central link of the **T** represents the inter-arytenoid notch, and the transverse link represents the chink between the epiglottis and the arytenoid masses. The epiglottis somewhat overhangs the slit in front, but is *not* folded down on to it. The slope of the arytenoid cartilages behind leads down to the narrow lower end of the pharynx.

In this movement the arytenoid cartilages are tilted forward and downwards, with relaxation of the posterior crico-arytenoid muscles. The vocal cords are depressed and relaxed, and the aryteno-epiglottic folds form an acute angle at the top of the pyriform fossa on each side.

When the opening of the larynx is closed and held up in this position, the food which is passed back into the pharynx does not come into contact with the closed aperture at any time. The food bolus is pushed out into the pharynx by the upward and backward pressure of the tongue, and this probably somewhat overhangs the epiglottis and the closed aperture behind and below it, so that the bolus, passing down behind the tongue, only just touches the arytenoid slope.

Extrinsic Movement.—The larynx is raised as a whole immediately the bolus of food passes the fauces, mylohyoid, thyro-hyoid, the palato-glossal, palato-pharyngeal, and pharyngeal muscles being concerned in the movement. The closed opening into the larynx is probably still further protected by the overhanging epiglottis by this co-ordinated movement.

SECTION VII.

RESPIRATION.

CHAPTER XXIV.

THE NEURO-MUSCULAR MECHANISM OF RESPIRATION.

THE respiratory tract consists of the nose, the naso-pharynx, the larynx, the trachea, the bronchi, and finally the bronchioles which open into the air sacs or lung infundibula.

The inner surface of the trachea is lined by columnar ciliated epithelial cells, amongst which there are many goblet cells. Beneath the basement membrane, on which these cells rest, there are many mucous glands, the ducts of which open between the surface epithelial cells. The mucus secreted by these glands and the goblet cells keeps the surface lining of the trachea moist, and by this means dirt particles which enter with the inspired air are caught on the tracheal walls and become eventually carried upwards, entangled with the mucus, by the movements of the cilia of the columnar cells.

The trachea is about 4½ inches long. Its lower end is fixed in position and opposite the level of the upper border of the fifth dorsal vertebra; it divides into the right and left bronchi. Each bronchus divides into smaller bronchi, and these eventually break up into bronchioles. In their turn the bronchioles open into the air sacs or infundibula of the lungs; on the walls of each infundibulum are the lung alveoli.

THE ELEMENTS OF THE LUNGS.

These consist of a bronchiole opening into an infundibulum or air space, on the walls of which are the air alveoli.

Each bronchiole is lined by a cubical epithelium supported by a thin basement membrane, outside which is a wall of unstriped muscle, the fibres of which are arranged in a circular manner. This muscle is innervated by the vagus. It is possible that the function of the muscle of the bronchiole is to regulate the quantity of air which enters the infundibulum, and also to regulate the tension of the air present in the infundibulum. If the tone of the bronchiole muscle remains constant during inspiration and expiration, as the lung expands during inspiration, the tension in the infundibulum remaining fairly constant, the effect of the inspiratory movement must consequently be to cause the capillaries in the wall of the infundibulum to become distended, so that at the end of inspiration they will contain their full complement of blood, and therefore increase the ease of oxidation of the blood. It is generally believed that adrenalin has no effect on the calibre of the pulmonary arterioles, and it is therefore surmised that these vessels have no vaso-motor nerves in their walls:

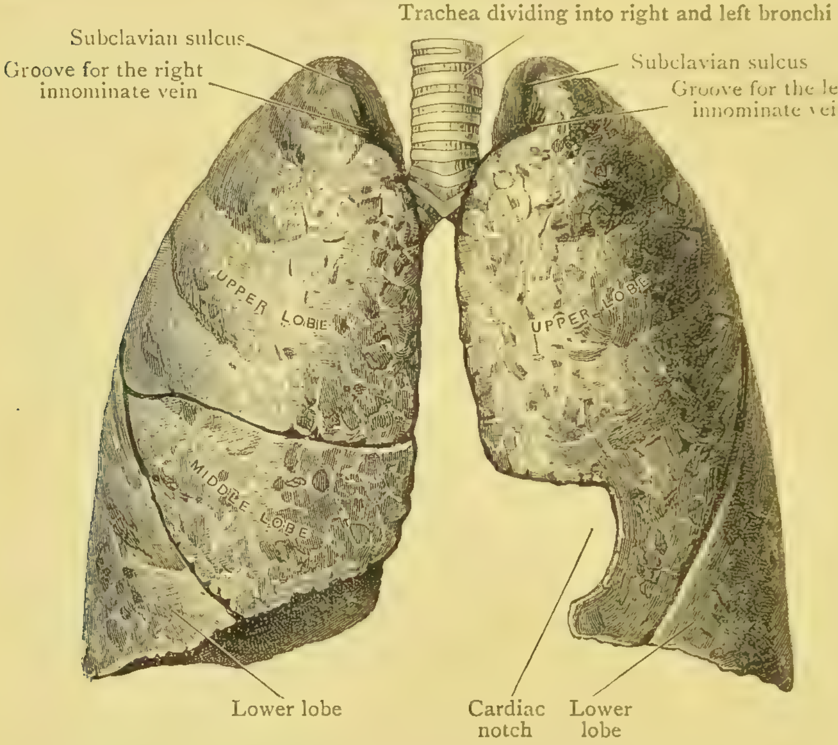

Trachea dividing into right and left bronchi
Subclavian sulcus
Groove for the right innominate vein
Subclavian sulcus
Groove for the left innominate vein
UPPER LOBE
UPPER LOBE
MIDDLE LOBE
Lower lobe
Cardiac notch
Lower lobe

FIG. 43.—The trachea, bronchi, and lungs of a child, hardened by formalin injection. (Cunningham.)

that is, the pulmonary arterioles are not directly under the control of the autonomic nervous system,—in other words, the amount of blood traversing the lung capillaries is regulated by mechanical, that is respiratory, influences. It is possible, therefore, that the unstriped muscle of the bronchioles indirectly regulates the amount of blood flowing through the lung capillaries by controlling the tension of the air in the infundibula.

The infundibulum is the funnel-shaped air sac into which the bronchiole opens, and on its walls are the alveoli of the lung. The infundibulum is the essential expansile part of the lung. When the lung is in the position it acquires during expiration, the infundibula are smaller and the alveoli more rounded. When the lung is in the position of inspiration, the infundibula are larger, *i.e.* distended, and the alveoli are opened out. The alveoli are lined with flattened cubical cells (not endothelial cells), which on the one side are in contact with alveolar air, and on the other with the endothelial walls of the pulmonary capillaries. In the connective tissue of the lungs there is much yellow elastic tissue, which by its elastic recoil aids expiration. In emphysema of the lung, this tissue,

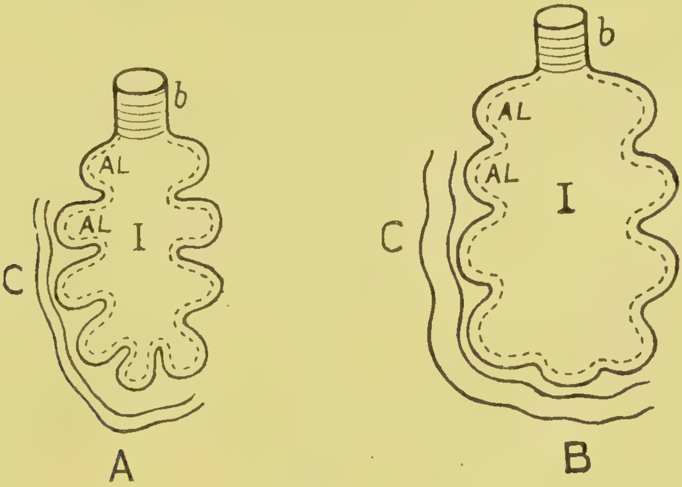


FIG. 44.

A, represents an infundibulum of the lung at the end of expiration. *b* is the bronchiole surrounded by plain muscle. I, the infundibulum with the alveoli (AL) opening into it. The alveoli are lined by flattened cubical cells. The capillaries (C) contain a comparatively *small* amount of blood.

B, represents an infundibulum of the lung at the end of inspiration; *b*, the bronchiole, governed by the plain muscle, remains the same size as in A; I, the infundibulum distended, and the alveoli AL, are opened out somewhat. The capillaries (C) contain a comparatively *large* amount of blood. It will be seen that the pulmonary capillaries are most dilated when the infundibulum is most distended with air.

to a considerable extent, loses its elasticity, and, as a consequence, the period of expiration is somewhat prolonged. The infundibula are, as a rule, larger on the free surface of the lung than in the interior, and those which are present on the anterior and superficial parts of the lung are more easily distended than those on the posterior and in the deeper portions.

THE EXTENSIBILITY OF THE LUNGS.

The inner surface of the thoracic cavity is covered with the pleura, the membranes of which are reflected over the lungs. The chief function of the pleura is to diminish friction between the lungs and the thorax wall during respiratory movement. At the same time, they allow more equal distension of the surface infundibula of the lungs during inspiration. The lungs are not uniformly extensible all over. During inspiration they appear to open out somewhat like a Japanese fan. From the anatomical point of view the lung may be divided into three zones. The innermost, or root zone, which contains the bronchus, pulmonary artery and vein, lymphatics and lymphatic glands, with a certain amount of connective tissue; this portion is least extensible. The intermediate zone, which consists of the smaller bronchi and the ramifications of the blood vessels with some true pulmonary tissue; this portion is more extensible than the innermost zone. It contains more pulmonary tissue. The outer zone, which is about 30 mm. deep, chiefly contains the infundibula, and is by far the most extensible portion.

During inspiration, however, the surface or sub-pleural infundibula do not uniformly expand all over. According to Keith, there are two surfaces of expansion: (1) The surface of direct or great expansion, which includes the *sterno-costal* and *diaphragmatic* surfaces of the lung; and (2) the surface of indirect or less expansion, which includes the *apex* of the lung, which is in contact with Sibson's fascia at the root of the neck; also the *dorsal* surface of the lung, which is in contact with the vertebræ and the spinal segment of the ribs, to which the fibres of the erector spinæ are attached; and also the *mediastinal* surface in contact with the pericardium.

TWO PHASES OF THE RESPIRATORY PROCESS.

These are **inspiration**, brought about by the contraction of certain muscles, which causes the thorax to enlarge and the lungs to expand, and, as a result, the tidal air (300 c.c.) is drawn into the trachea and bronchi; and **expiration**, which is also brought about most probably by the contraction of muscles which are antagonistic to those of inspiration. Sherrington has shown that there is a reflex co-ordination between antagonistic groups of muscles in the body generally, and this most probably also holds good for the groups of respiratory muscles.

If the diaphragm and ribs co-operate during quiet inspiration, the lung expands in three chief directions—downwards, forwards, and outwards—and to a certain extent the roots of the lungs share in this movement. If the breathing is of the abdominal type, due chiefly to contraction of the diaphragm, the roots of the lungs and the heart descend; this is the type of respiration which occurs in men. On the other hand, if the breathing is of the thoracic type, that usually present in women because of the use of corsets, the roots of the lungs and the heart move slightly forward towards the sternum.

The Osseo-muscular Mechanism of Inspiration.—During inspiration groups of muscles contract in a co-ordinated manner, and cause movements of the ribs, sternum, and vertebræ, which result in the enlargements of the bony thorax, with the effect that the lungs expand. Keith divides the thorax into four portions:

1. The thoracic operculum.
2. The upper costal series covering the upper lobes ot the lungs.
3. The lower costal series covering the lower lobes of the lungs; this includes the diaphragm.
4. The floating ribs, which may be taken as part of the abdominal wall.

Movements of the Diaphragm and the Lower Costal Series.—The diaphragm consists of two parts,—the *spinal or crural portion*, which is attached to the back portion of the central tendon; its action is to draw the central tendon in a downward direction. The *costo-sternal portion, or anterior part*, which is attached to the front and sides of the central tendon ; the action of this portion is to draw the central tendon downwards and somewhat forwards. The total action of the diaphragm is therefore piston-like, and, when the two sets of fibres contract together, the contents of the abdomen are driven downwards and forwards.

The lower costal series includes the sixth, seventh, eighth, ninth, and tenth ribs, and their external intercostal and interchondral muscles. These structures cover over the lower lobe of the lung, and are designed for the expansion of this lobe. In bringing this change about, the diaphragm is the all-important muscle, aided to a certain extent by the ilio-costales. The result of its action is to cause the lower portion of the sternum to move forwards, so that the thorax increases antero-posteriorly, the ribs are rotated slightly outwards, and this increases the transverse diameter of the thorax, and in its downward movement the vertical diameter of the whole cavity is increased. As the lower portion of the thoracic cavity increases in its three diameters, the lower lobe of the lung glides beneath the ribs and thus expands.

The antagonistic muscles to the diaphragm, the ilio-costales, external intercostals, and the interchondrals, are the external obliques, internal obliques, the transversales, and the internal intercostals ; these may be considered as muscles which bring about expiratory movements.

THE THORACIC OPERCULUM.—The operculum of the thorax includes the first dorsal vertebra, the first ribs, and the manubrium sterni. During inspiration there is a slight upward movement of the operculum, which causes slight expansion of the anterior or ventro-lateral part of the apex of the lungs. As a rule, in those persons who follow a sedentary occupation and have an ill-developed thorax, there is very little movement of this portion of the thorax during respiration. The manubrium articulates with the main part of the sternum at the manubrio-sternal joint, and in those who have the thoracic type of respiration there is free respiratory movement at this joint. The operculum and its muscles, which are attached above, form a fulcrum towards which the upper set of ribs may be raised during inspiration.

MOVEMENTS OF THE UPPER COSTAL SERIES.—This portion of the thorax consists of the second, third, fourth, and fifth ribs, and their intercostal muscles, together with the mesosternum, and covers over the upper lobes of the lungs. The fissure separating the upper from the lower lobe of the lung corresponds with a line drawn round the thorax from the head of the second rib to the sixth costal cartilage. During life the upper lobe of the lung lies against the second to the fifth ribs and their costal cartilages, and follows the movements of this portion of the thorax. Here there is no gliding movement of the lung against the chest wall. During inspiration these ribs, by the external and internal intercostals, which work together, are drawn up towards the operculum, which acts as a fulcrum. During inspiration, both sets of intercostals here are tense. During expiration the lower costal series is fixed by the abdominal muscles, as already stated, and this affords a fixed base towards which the upper costal series may be depressed. The intercostal spaces are not so wide, the sternum is drawn slightly down, and the upper lobe of the lung consequently becomes smaller. It may be concluded, then, that the upper costal series is drawn *up* towards the operculum during inspiration, and *down* towards the lower costal series during expiration; and, as the upper lobe of the lung is, in normal circumstances, *against* this portion of the thorax, this lobe must necessarily follow the thoracic movements.

THE MOVEMENTS OF THE FLOATING SERIES.—The tenth and eleventh intercostal spaces widen during inspiration and diminish during expiration. The last rib is fixed by the quadratus lumborum, the erector spinæ, and a ligamentous membrane derived from the middle layer of the lumbar fascia, and this anchors the lower border of the last rib to the transverse process of the first and second lumbar vertebræ and the iliac crest. This helps to bind the lower ribs at and near their angles to the vertebræ and the ilium, and in this way more or less fixes them, so that in moderate action of the diaphragm they are not drawn inwards.

The Influence of the Erector Spinæ and its Prolongations.—These deep muscles of the back, by producing extension of the spine, cause an increase in all the diameters of the thorax during inspiration.

Expiration is brought about, as has been already stated, by the contraction of certain muscles which are antagonistic to the diaphragm and its accessories, but there is no doubt that elastic recoil assists the process of expiration. The lungs contain a large amount of yellow elastic tissue, and the bronchi and bronchioles contain unstriped muscle, and it is to these tissues that the tendency of the lungs to collapse, or their contractility, is due. It is this contractility of the lungs which causes them to exert a pull on, or to tend to recede from, the thorax wall. In this way a negative pressure in the pleural cavity is produced. It has been ascertained that the negative pressure in the thorax of a corpse is – 6 mm. Hg; that is, at the end of *extreme* expiration there is a negative pressure in the pleural cavity due to the elasticity of the lungs. After a full inspiration, when the elastic tissue is on the stretch, the negative pressure in the pleural cavity is as much as – 30 mm. Hg. In the morbid condition known as emphysema, the elastic tissue of the lung degenerates, the negative pressure in the pleural cavity becomes diminished, and expiration is consequently prolonged. It is possible, too, that there is some elastic recoil from the abdominal viscera and their contained gases, for these are compressed during the downward and forward movement of the diaphragm.

The constant negative pressure which occurs in the thorax is an important factor in aiding the venous blood flow into the thorax, and therefore indirectly in bringing about the arterialisation of the blood.

During inspiration the vocal cords are abducted, whereas during expiration they are somewhat adducted.

The Graphic Record of the Respiratory Movements.—The instrument used for this purpose is a stethograph, the receiving tambours of which are fastened to the chest. A lever with a writing point is connected with the recording tambour. In this way a record of the respiratory movements may be taken upon a revolving smoked drum. Respiratory movements are readily affected by efferent nervous impulses; the subject of the experiment must therefore not be allowed to see the movements of the recording lever.

THE NERVOUS MECHANISM OF RESPIRATION, TOGETHER WITH THE CHEMICAL FACTOR.

The muscular mechanism of respiration is directly under the control of the central nervous system. The nervous mechanism may be considered under the three headings—

1. The respiratory centre;
2. Afferent impulses which influence the centre; and,
3. Efferent impulses which leave the centre.

The Respiratory Centre, or **Nœud Vitale**, is situated in the lowest part of the floor of the fourth ventricle at the calamus scriptorius. It consists of two halves symmetrically placed on either side of the middle line; and the nerve cells, constituting the centre, are in all probability connected across the middle line by commissural fibres. Each half of the centre appears to consist of two parts, the *inspiratory* and the *expiratory* portions, the latter being as active as the former, but being especially called into activity when the mucous membrane of the larynx is stimulated, and when prolonged expiratory blasts occur. The lower limit of the centre has been defined in animals by cutting away thin slices of the medulla oblongata from above downwards. When the lowest limit of the centre is reached the animal stops making any respiratory movement. The upper level of the centre may be defined in a similar way, the sections being made from below upwards. When the lowest section is made the thoracic respiratory movements stop, but the dilatores nares still contract; when the upper limit of the centre is reached these muscles become paralysed.

THE PHYSIOLOGY OF THE RESPIRATORY CENTRE.—1. The respiratory centre is an *automatic* one, acquiring its energy from the nutrition and from oxygen supplied to it through the blood. The centre, however, exhibits a specific irritability for CO_2, and, should the pressure of the CO_2 in the blood rise beyond normal, the respiratory centre is so stimulated that respiratory movements are increased in *depth*; this alteration occurs in order that there may be exercised elimination of CO_2 from the lungs, and the pressure of CO_2 in the blood consequently diminished. Normally the air in the alveoli contains 5 per cent. CO_2; if this percentage rises the CO_2 pressure is raised in the blood, consequently there is increased stimulation of the respiratory centre, with the result that pulmonary ventilation is correspondingly increased, and the excess of CO_2 got rid of. It is this rise of CO_2 tension in the blood which most probably starts the normal respiratory movements in the newly born child. So long as the blood of the fœtus is oxygenated through the placenta there is no call upon the respiratory centre. During the birth of the child the contractions of the uterus interfere with the placental respiration, the CO_2 pressure rises in the blood of the child, and the respiratory centre is consequently stimulated.

This will account for the fact that the child may make respiratory efforts *during* the passage of its head through the vaginal canal, even before the head is delivered.

If a man rapidly takes a number of deep breaths, apnœa follows; this is due to the fact that the CO_2 in the lung alveoli, and consequently that in the blood stream, has been swept out of the body, and it is therefore not present in the blood at sufficient pressure to stimulate the respiratory centre. The centre is also influenced by the accumulated products of metabolism. If the muscles of an animal are tetanised the respiratory centre becomes more active; this may be due to the influence of nitrogenous katabolites, as well as to an increased CO_2 pressure. The centre is also influenced by the temperature of the blood flowing through it. If the temperature is raised, respiratory movements are increased in frequency, in order that more heat may be lost by the expired air. Drugs in the blood influence the respiratory centre, *e.g.* opium and morphia depress, whereas strychnine increases the activity of the centre.

2. The respiratory centre is a *reflex* one, depending upon afferent impulses which arrive from the lungs through the vagi. This fact has been proved by Head's experiment on the diaphragm of a rabbit. After the animal has been anæsthetised a tube is tied in its trachea. The abdomen is opened just below the ensiform cartilage, and one of the pieces of muscle belonging to the anterior part of the diaphragm partially detached. This can be done without interfering with the action of the diaphragm, and the nerve and blood supply of the piece of partially detached muscle can be kept intact. The free portion of the muscle is then brought out of the abdominal wound and fixed to a recording lever. A record of the contractions of this piece of muscle (and consequently of the diaphragm) can then be taken. If the lungs are artificially distended, *i.e.* positive ventilation produced, by blowing into the tracheal tube, it is found that the diaphragm becomes relaxed. The conclusion which is drawn is that, when the infundibula are in a state of distension, afferent impulses travel from the lungs up the vagi, which inhibit the activity of the inspiratory part of the respiratory centre, impulses no longer travel down through the phrenic nerves, the diaphragm consequently becomes relaxed. If the lungs are made to acquire the position of forced expiration by the

withdrawal of air, *i.e.* negative ventilation performed, it is found that the diaphragm contracts. This is due to the more or less collapsed condition of the lungs, causing afferent impulses to travel up the vagi to the inspiratory part of the respiratory centre, which increase its activity, the result of which is that the centre gives out impulses which descend in the phrenic nerves, causing the diaphragm to contract. It is concluded, then, that alternately two sets of impulses ascend the vagi from the lungs. When the lungs are in the position of inspiration, impulses travel up which inhibit the activity of the inspiratory part of the respiratory centre, and expiration follows. When the lungs are in a position of expiration, impulses ascend the vagi which reflexly bring about inspiration by increasing the activity of the inspiratory part of the respiratory centre.

It has been contended by Gad, however, that only one set of impulses travels from the lungs up the vagi to the respiratory centre, and the influence of these is to inhibit the activity of the inspiratory centre, and consequently to produce expiration. In favour of this view is the fact that, if the two vagi, in an animal under an anæsthetic, are divided so as to cut off the afferent impulses from the lungs, there is increased inspiratory tone.

It will be seen also that afferent impulses from other parts of the body influence the respiratory centre (*vide* p. 326).

3. The respiratory centre is a *rhythmic* centre,—that is, it sends out impulses in a rhythmic manner. The vagi regulate the rhythmic power of the centre, and consequently the rhythm of respiratory movements. If the vagi are divided, respiratory movements still go on, but the rhythm is altered and the movements become much slower. The increased activity of the nerve cells, constituting the inspiratory centre, is the result of katabolic changes or oxidation changes. Following this activity, rest results, during which anabolic changes occur, and energy is stored, to be followed later by increased activity. This rhythmicality varies according to age: young children breathe forty times per minute, adults eighteen times per minute. This rhythmicality also varies with varying circumstances,—children during sleep, and adults just before death, exhibit an altered rhythmicality known as Cheyne-Stokes respiration. In this condition shallow respiratory movements are followed by those which become

deeper and deeper, which are again followed by shallower and shallower movements, as shown in Fig. 45. Hibernating animals, such as the dormouse, during their winter sleep, also exhibit this altered rhythmicality, though the breathing is slightly modified as compared with that of the human being. This is shown in Fig. 46. This altered rhythm of the respiratory centre has been compared with a similar condition which occurs in the vasomotor centre when it is giving out. The curves which demonstrate this change on a blood-pressure tracing are known as Traube-Hering waves.

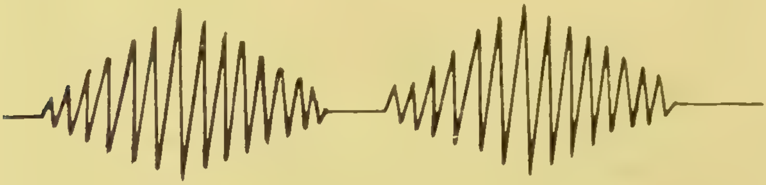


FIG. 45.—Diagram to represent the respiratory movements of Cheyne-Stokes respiration.

4. The respiratory centre is an *involuntary* centre, though there is a certain amount of voluntary control from the cortex cerebri. The control affects the rate and depth of the respiratory movements, though complete inhibition is impossible. When a person is listening intently, as a rule, the "breath is held," *i.e.* respiratory movements are completely inhibited for a short period. If one wishes to count the number of respirations of a patient, the patient should be kept unaware of the fact, otherwise the respiratory movements are almost invariably found to be quickened.

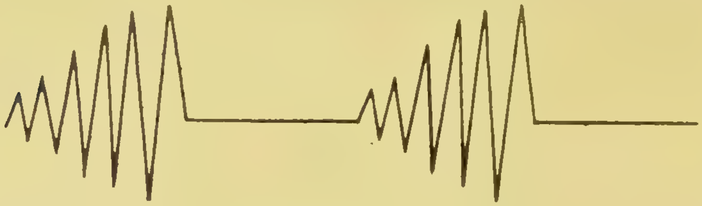


FIG. 46.—Diagram to represent Cheyne-Stokes respiration in a hibernating animal.

Afferent Impulses which influence the Respiratory Centre.

(*a*) These travel chiefly through the vagi. If copper wires, previously cooled by placing one end in a freezing mixture, are placed under the vagi, the nerves become paralysed without previous excitation. The effect is that, as afferent impulses are cut off, respiratory movements become slower. If the central end of one of the nerves is then faradised with a current of medium strength, respiration become quicker, and there may be at length an inspiratory spasm.

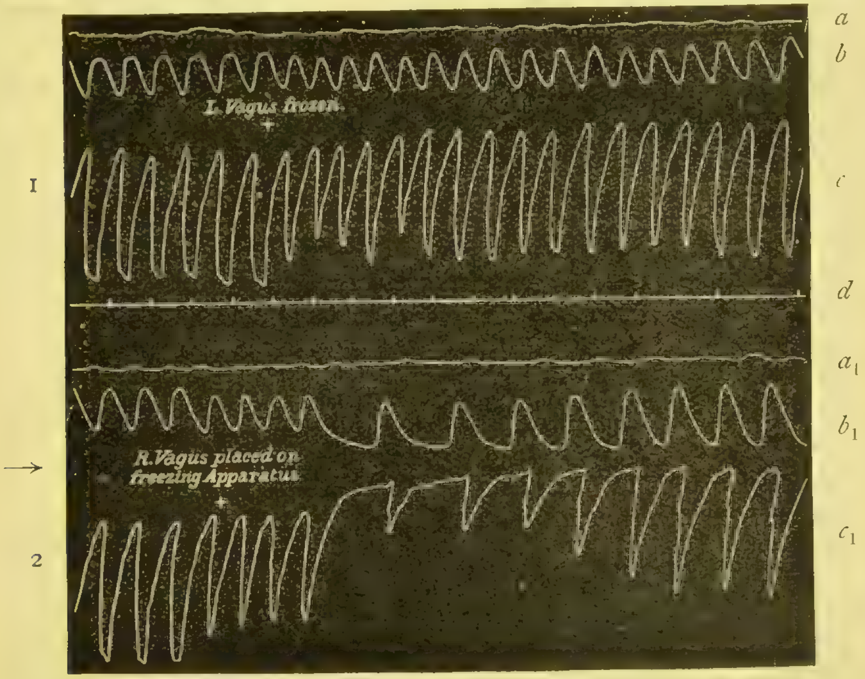


FIG. 47.—The effects on respiratory movements of freezing first one vagus, then the other. (Head.)

a, a_1 = Control tracing, showing *passive* movements of the chest wall.
b, b_1 = Tracing taken by a tambour, showing the changes in pressure in a bottle of air connected with the trachea.
c, c_1 = Myogram of diaphragmatic slip.
d = Time record marking seconds.

If a weak faradic current or a constant ascending current is employed, the *expiratory* muscles are reflexly brought into play.

(*b*) The *superior laryngeal* branch of the vagus conveys impulses to the respiratory centre. If the nerve is cut, and the upper cut end faradised, inspiration is inhibited, and a spasmodic and forcible expiration follows. If a crumb gets into the upper part of the larynx it mechanically stimulates the mucous membrane, with the result that inspiration is inhibited, so that it is drawn in no further; spasmodic and forcible expiratory blasts, that is, coughing, follow, and the irritant is consequently expelled.

(*c*) *Stimulation of the upper cut end of the glosso-pharyngeal nerve* causes inhibition of respiratory movements. This occurs during swallowing, and is doubtless a special provision to guard the respiratory passages from the presence of food particles.

(*d*) *Stimulation of the skin*, which results in sensations of cold or pain, causes increased activity of the inspiratory centre. If at birth a child does not breathe, it may be made to do so by the application of cold and painful stimuli, such as a smart slap from a wet towel. In cases of opium poisoning, when the activity of the respiratory centre is failing, it may be stimulated by flicking the calves of the individual with a cold wet towel, or by applying a strong faradic current to the skin.

(*e*) *Mechanical stimulation of the splanchnic nerves*, as by tapping the exposed intestines of an animal, will frequently cause a temporary arrest of respiratory movements. This happens when an individual has been "winded" by a blow over the upper part of the abdomen.

(*f*) *Stimulation of the walls of the external auditory meatus*, such as occurs when a plug of wax is present, frequently results in spasmodic expiratory blasts, *i.e.* reflex ear cough. This is due to irritation of the fibres of the auricular branch of the vagus (Arnold's nerve). In a similar manner stimulation of the mucous membrane of the trachea, bronchi, and stomach reflexly produces coughing; the last is frequently known as stomach cough.

(*g*) When there is any *mechanical stimulation of the mucous membrane of the nose* (second division of fifth nerve), and occasionally, when a hypersensitive retina is exposed to a bright light, reflex spasmodic expiratory efforts known as sneezing occur.

(*h*) As already stated, afferent impulses may travel from the cerebral cortex to the respiratory centre, which, within certain limits, may control its working with regard to the frequency and depth of the respiratory movements.

Efferent Impulses leave the Respiratory Centre.—These travel down the lateral columns of the spinal cord, and leave by the anterior nerve roots. The fibres which bring down the impulses probably make cell stations in the anterior cornual cells. Those impulses, which travel down in the phrenic nerve, leave the spinal cord at the level of the third, fourth, and fifth cervical segments. If the spinal cord is injured just below the fifth cervical segment, respiration may still go on by means of the impulses, which leave by the phrenic nerve, and which are carried down to the diaphragm (abdominal respiration). Other impulses leave the anterior nerve roots in the dorsal region of the spinal cord, and travel out in the intercostal nerves, getting thence to the intercostal and abdominal muscles. Efferent impulses also proceed by the vagi through the recurrent laryngeal nerves to the posterior crico-arytenoid muscles, which abduct the vocal cords and cause the glottis to widen during inspiration.

The vagi also carry down impulses which go to the lungs; these impulses are of two kinds—*Trophic* to the lung tissue (*vide* p. 572) and *Bronchomotor*.

If both vagi are injured, sooner or later degenerative changes occur in the lung tissue resulting in trophic pneumonia, and death subsequently follows. It is believed, therefore, that the vagi control the nutrition of the lung tissue.

Fibres from the vagi supply the unstriped muscle in the walls of the bronchial tubes and in the bronchioles. If a lobe of a lung is placed in a plethysmograph, artificial respiration kept up, and that portion of the vagus going to the lung cut, the bronchioles dilate somewhat and more air enters the lung. If the peripheral cut end of the nerve is faradised the bronchioles become smaller, and less air enters the lung. If a weak solution of muscarine is injected into the circulation, the volume of air entering the lung is decreased on account of the drug stimulating the vagus terminals and causing spasm of the muscular wall. If a weak solution of atropine is then injected into the circulation, the vagus terminals are paralysed, and more air enters the lung. Relaxation of the bronchiole muscles may also be brought about by the inhalation of chloroform or ether. The dyspnœa of spasmodic bronchial asthma is due to the spasmodic contraction of the muscle in the bronchioles, probably due to abnormal stimulation of the nerve cells at the origin of the vagi. Such spasm may be overcome by the use of anti-spasmodics, such as stramonium and belladonna, which act by paralysing for the time being the terminals of the vagi in the bronchial tubes.

It has already been stated that the vagi preside over the tone of the muscle in the bronchioles, and that this muscle directly influences the tension of the air in the infundibula, and indirectly the amount of blood traversing the pulmonary capillaries. It has been found that direct stimulation of the mucous membrane of the nose (second division of the fifth nerve) causes a reflex contraction of the muscle in the bronchioles, so that air is prevented from entering the lungs. In this way irritating fumes may be prevented from entering the lungs. If, on the other hand, the mucous membrane of the nose is hypersensitive, a slight stimulus may cause reflex spasm of the bronchiole muscles (spasmodic bronchial asthma).

CHAPTER XXV.

THE CHEMICAL CHANGES OF RESPIRATION.

THE following tables give approximately the composition of inspired and expired air :—

	Inspired Air.		Expired Air.	
Oxygen . . .	20·96	vols. per cent.	16·03	vols. per cent.
Nitrogen (argon 0·94, included with the nitrogen) .	79		79	
Carbon dioxide . .	0·04		4·4	
Water . . .	Varies		Saturated	
Temperature . .	Varies		37° C.	
Volume . . .	$\frac{50}{50} = 1$		$\frac{49}{50}$ (though the volume is apparently increased because the temperature is usually raised).	

As the inspired air passes through the nose it sweeps upwards and backwards over the mucous membrane which covers the superior and middle turbinated bones. It is then warmed and moistened by the watery secretion produced by the glands, which are embedded in the mucous membrane. It has been calculated that the inspired air gains two quarts of water in the twenty-four hours from the mucous membrane of the nose.

AIR VOLUMES.

Tidal air (the volume of air breathed at each respiration) .	500 c.c.
Complemental air (that which can be forcibly inspired after a normal inspiration)	1500 ,,
Supplemental air (that which can be forcibly expelled after a normal expiration)	1500 ,,
Residual air (that which remains in the lung infundibula after a forcible expiration)	2000 ,,

THE VITAL CAPACITY OF THE LUNGS.

If an individual takes a deep inspiration, expanding the lungs to the fullest possible extent, and then forcibly expires, he expels his complemental air (1500 c.c.), tidal air (500 c.c.), and supplemental air (1500 c.c.). The volume of this air may be measured by a spirometer, which thus shows the vital capacity of the chest. The vital capacity of a narrow-chested individual may be increased by training. It is found that the vital capacity varies with posture, being greatest when the body is erect and least when it is prone.

THE RESPIRATORY EXCHANGE.

The amount of oxygen taken into the body and the amount of CO_2 put out may be estimated by analysing continuous samples of air expired through a meter.

Such a calculation may be made as follows :—

The tidal air is 500 c.c., man respires say sixteen times a minute, therefore 8000 c.c. of air are respired per minute. Inspired air contains 21 per cent. oxygen and expired air 16 per cent.

$$\therefore \frac{21-16}{100} = \frac{5}{100} \times 8000 = 400 \text{ c.c. oxygen used per minute.}$$

Inspired air contains 0·04 per cent. carbon-dioxide, and expired air 4·4 per cent.

$$\therefore \text{ in round numbers } \frac{4{\cdot}4-0{\cdot}04}{100} = \frac{4}{100} \times 8000 = 320 \text{ c.c. } CO_2$$

discharged per minute.

It will be seen that the volume of carbon-dioxide discharged is less than the volume of oxygen retained. The relationship between the two is the respiratory quotient, or R.Q.

$$\text{Respiratory quotient} = \frac{\text{vol. of } CO_2 \text{ discharged}}{\text{vol. of } O_2 \text{ retained}} = \frac{320}{400} = \frac{4}{5} = 0{\cdot}8.$$

There is a certain proportion of oxygen retained in the body in order that the waste and harmful products of metabolism may be oxidised into comparatively inert substances, such as urea and uric acid, before they are excreted. Such retained oxygen does not appear in combination with carbon as CO_2.

The respiratory quotient varies with the nature of the food.

The products of digestion, after having been absorbed, eventually undergo oxidation somewhere in the body. It is found that, for a pure carbohydrate diet, the respiratory quotient becomes nearly 1, for a protein diet 0·8 and for fat 0·7.

According to M. S. Pembrey, the following formulæ represent the oxidation of carbohydrate, protein, and fat :—

GLUCOSE.

$$C_6H_{12}O_6 + 6\ O_2 = 6\ CO_2 + 6\ H_2O.$$

$$R.Q. = \frac{6\ CO_2}{6\ O_2} = \frac{6 \times 2}{6 \times 2} = 1\ (\textit{vide}\ \text{p. } 389).$$

ALBUMIN (Empirical Formula).

$$C_{72}H_{112}N_{18}O_{22}S + 77\ O_2 = 63\ CO_2 + 38\ H_2O + 9\ CO\ (NH_2)_2 + SO_3$$

$$R.Q. = \frac{63\ CO}{77\ O_2} = \frac{63 \times 2}{77 \times 2} = 0{\cdot}82.$$

OLEIN.

$$C_3H_5(C_{18}H_{33}O_2)_3 + 80\ O_2 = 57\ CO_2 + 52\ H_2O$$

$$R.Q. = \frac{57\ CO_2}{80\ O_2} = \frac{57 \times 2}{80 \times O_2} = 0{\cdot}71.$$

ALVEOLAR AIR.

Haldane and Priestley's method of obtaining alveolar air :—

The apparatus employed is shown in the following figure. It consists of an anæsthetic mask connected with a T-shaped glass tube, at the opposite end of which is a piece of india-rubber tubing about 4 feet long and 1 inch in diameter. Connected with the vertical limb of the T-shaped glass tube and about 2 inches from the mask, is a glass gas-sampler of capacity 50 c.c. This is connected with the T-shaped tube by a three-way tap. Before the experiment the gas-sampler must be rendered a vacuum. The subject of the experiment breathes normally through the anæsthetic mask, then after a normal inspiration he expires quickly and deeply, expelling tidal air + supplemental air. The tap of the gas-sampler is then opened, and a sample of the last portion of the expired air is collected and analysed. The subject now makes a normal expiration, after which he expires deeply, getting rid of supplemental air, which is collected and analysed. The mean result of the two analyses, *i.e.* of tidal air + supplemental air, and of supplemental air alone, gives approximately the mean composition of the air in the infundibula, and consequently in the lung alveoli.

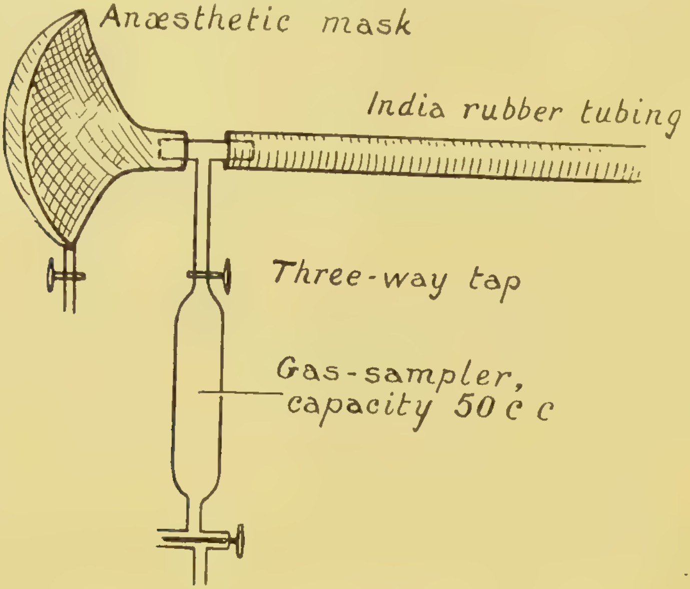


FIG. 48.—Apparatus for collecting alveolar air. (*After* M. S. Pembrey.)

Composition of alveolar air :—

Nitrogen	79 per cent.
Oxygen	13–14 ,,
Carbon-dioxide	5–6 ,,

THE GASES OF THE BLOOD.

The amount of oxygen and of carbon-dioxide contained in the blood depends upon three factors :

(*a*) The solubility of these gases in the blood plasma.

(*b*) The partial pressure or tension of the gases exposed to the plasma.

(*c*) The chemical affinity which salts in solution, substances in colloidal solution, such as proteins, and bodies suspended in the blood, such as the erythrocytes, have for the gases.

The gases contained in the blood may be obtained by introducing a given quantity of blood (arterial or venous) into a vacuum, and gently warming the vessel which contains the blood by holding it in the hands. Such a vacuum may be obtained by using either Pflüger's or Leonard Hill's mercurial air-pump. The total volume of gas obtained from a given quantity of blood is first measured. The further analysis of the gas is made by using Waller's modification of Zuntz's gas analysis apparatus, by which the CO_2 is absorbed by KOH and the O by phosphorus (or pyrogallic acid); the residual gas is N.

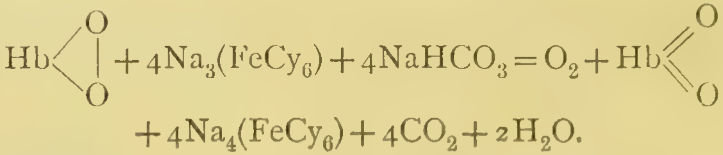
It is found that one hundred volumes of blood yield about sixty volumes of gas, which are constituted as follow :—

	O Vols.	CO_2 Vols.	N Vols.
100 vols. of arterial blood yield	20	40	1 at 0° C. and 760 mm. Hg.
100 vols. of venous blood yield	12	48	1

It will be understood that the analysis above involves the examination of large quantities of blood. When small quantities of blood are to be examined for the contained gases, the apparatus devised by Barcroft is generally used (*vide* Fig. 49). This consists of two glass tubes A and B, each connected with a glass reservoir C containing water, and this latter is connected with a rubber reservoir D also containing water, the pressure in which may be regulated by the spring E.

The tube A is open to the atmosphere, B is closed by a cork, but connected by a side tube with a bottle F. If it is required to ascertain the amount of oxygen contained in the blood, the experiment is conducted as follows :—

Five c.c. of blood are placed in the bottle F and covered with a dilute solution of ammonia. The bottle is gently shaken in order to lake the blood. A saturated solution of ferricyanide of potassium is placed in the vessel G, which is subsequently upset into the laked blood; while this is being done the vessel F is placed in a water bath at room temperature. The ferricyanide of potassium expels the oxygen (respiratory oxygen) from the oxyhæmoglobin, and then the hæmoglobin so formed combines with sodium bicarbonate to form the stable compound methæmoglobin. The following equation appears to represent the chemistry of the process :—



$$\mathrm{Hb}\left<\begin{matrix}\mathrm{O}\\ |\\ \mathrm{O}\end{matrix}\right. + 4\mathrm{Na_3(FeCy_6)} + 4\mathrm{NaHCO_3} = \mathrm{O_2} + \mathrm{Hb}\left<\begin{matrix}\mathrm{O}\\ \\ \mathrm{O}\end{matrix}\right. + 4\mathrm{Na_4(FeCy_6)} + 4\mathrm{CO_2} + 2\mathrm{H_2O}.$$

$\mathrm{Hb}\left<\begin{matrix}\mathrm{O}\\ |\\ \mathrm{O}\end{matrix}\right.$ represents oxyhæmoglobin, and $\mathrm{Hb}\left<\begin{matrix}\mathrm{O}\\ \\ \mathrm{O}\end{matrix}\right.$ methæmoglobin; for it is held that the oxygen is united more firmly with hæmoglobin in oxyhæmoglobin than in methæmoglobin.

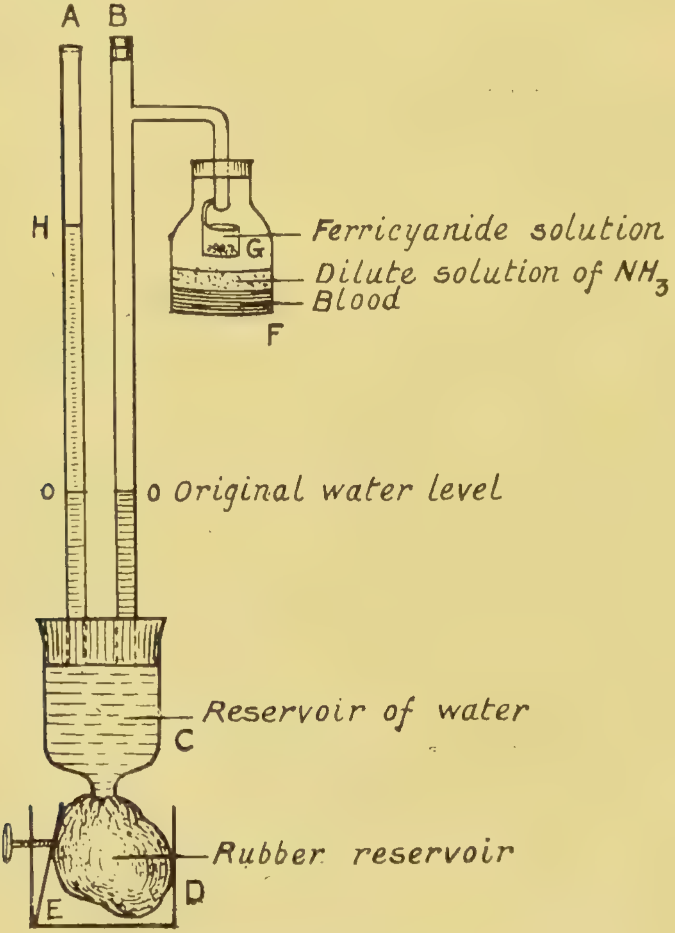


FIG. 49.—Barcroft's apparatus for obtaining the gases of the blood.

The oxygen set free from the oxyhæmoglobin displaces some of the air previously present in the bottle F, and this displaces air in the tube B; this air displaces water from the tube B, which, at the commencement of the experiment, stood at the level O. The water is now driven back in the tube B by squeezing the rubber reservoir until the level of the water is once more at O, at the same time water in the tube A rises to H. From the column of water OH the volume of oxygen liberated from 5 c.c. of blood can be deduced.

After the amount of oxygen has been determined the carbon-dioxide may be measured as follows :—Into the vessel G a solution of tartaric acid is placed, which is subsequently upset into the mixture consisting of blood, ammonia, and ferricyanide of potassium. The greater part of the carbon-dioxide which is liberated may be shaken out of the fluid. It must be remembered, however, that a small quantity always remains in the solution. The CO_2 which is liberated is measured in precisely the same way as the oxygen.

The Tension of the Gases in the Blood.—The tension or partial pressure of the gases in the blood may be ascertained by using an aërotonometer.

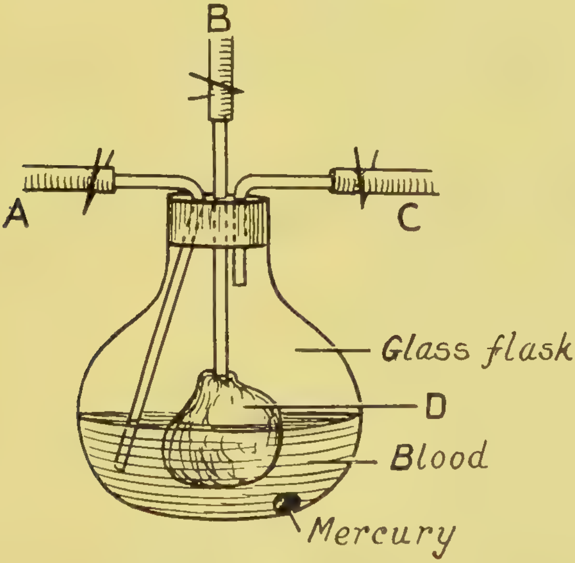


FIG. 50.—Loewy's aërotonometer. (*After* Halliburton.)

A = Tube for introducing or expelling the blood.
B = Tube connected with an indiarubber bag D, which contains water.
C = Tube for introducing or expelling the gas.

The aërotonometer of Loewy consists of a glass bottle with an arrangement of glass tubes passing through the indiarubber stopper. Each glass tube is provided with a piece of indiarubber tubing which may be closed by a clip.

Should it be required to determine the tension of the CO_2 in the blood, the following is the method to be adopted :—

At least three aërotonometers are required. The bag D is previously filled with water, and into each instrument gas containing a *known* percentage of CO_2 is introduced through C.

Into each aërotonometer blood from an animal is drawn through A. This is done by connecting A with a cannula placed in one of the blood vessels of an animal and withdrawing water from the bag D through B. Each bottle is shaken; during this process the blood is defibrinated by means of the mercury contained in the bottle, and equilibrium is established between the gases contained in the blood and those contained in the space in the aërotonometer above the blood. The tube C is then attached to an air-analysis apparatus, and water forced into the bag D in order to expel the gas from the aërotonometer.

The following figures, after Halliburton, illustrate results which might be obtained :—

Aërotonometer.	I.	II.	III.
Initial percentage of CO_2 present	6·0	5·0	4·0
Final percentage of CO_2 present after shaking with blood	5·8	5·1	4·3

It will be noted that in flask I. the blood has taken up CO_2 from the bottle, whereas in flasks II. and III. the blood gave up CO_2 to the gas. The tension of the CO_2 in the blood, therefore, is between 5·8 and 5·1 of an atmosphere of CO_2. It must be remembered that the tension (or pressure) of a gas *dissolved* in any fluid is equal to the pressure of the same gas in an atmosphere with which the gas, dissolved in the fluid, would be in equilibrium.

The tension of O in the arterial blood of man is given as 38·5.

The tension of CO_2 is given as follows :—

In the tissues	5 to 9	in the dog.
In venous blood	5·4	
In alveolar air	3·5 (in man 5·0)	
In expired air	2·5	
In arterial blood	2·8	

RESPIRATORY CHANGES IN THE LUNGS.

EXTERNAL RESPIRATION.

1. **Oxygen.**—During a normal inspiration atmospheric air is drawn into the larger bronchi; here the tension of the oxygen is greater than the tension of that oxygen which is in the infundibula, so that oxygen diffuses down from the bronchi into the infundibula, where the oxygen tension in man has been calculated to be 13 per cent. of an atmosphere of oxygen.

The gases in the infundibula, and consequently in the alveoli, are separated from the blood plasma in the lung capillaries by the flattened cubical epithelium of the alveoli and the endothelium lining the capillaries; it is believed that oxygen diffuses from the alveoli through the two kinds of epithelium into the plasma of the venous blood which has just arrived in the lung, and which is collected in the distended capillaries. (It has been already stated that, at the height of inspiration, the capillaries of the lung are fully distended with venous blood.) Now, oxygen accumulates in the blood, which is consequently becoming rapidly arterial, until its tension rises to 38·5. It is obvious, therefore, that there must be another factor at work besides diffusion to account for this difference of oxygen tension. The epithelium which lines the alveoli is cuboidal in shape, and was originally derived from the epithelium lining the alimentary canal, and in function it is probably secretory. Haldane has shown that the swim bladder of a fish, which is lined with a secreting epithelium, contains more oxygen than can be accounted for by its diffusion from the water into the bladder. It must be remembered, too, that water holds a comparatively small amount of oxygen in solution. The cells of the swim bladder probably actively secrete oxygen, and in this they are controlled by the vagus nerve; for it is found that, when the vagus is divided, there is no longer this storage of oxygen in the swim bladder. The inference to be drawn, therefore, is that some oxygen diffuses from the alveoli into the plasma of the lung capillaries so long as the oxygen in the alveoli is at a higher tension than that in the plasma; when, however, a state of equilibrium is reached, the cubical cells, possibly controlled by the vagi, begin to secrete oxygen from the alveoli into the blood plasma.

The oxygen of the plasma is rapidly taken up by the hæmoglobin present in the erythrocytes, to form an unstable compound, oxyhæmoglobin. It is found that the amount of oxygen which blood is capable of holding depends upon the amount of hæmoglobin present. There is sufficient hæmoglobin in 100 c.c. of arterial blood to hold 20 c.c. of oxygen in chemical combination as oxyhæmoglobin; the same volume of blood holds only 0·3 c.c. of oxygen in simple solution in the plasma. It is the hæmatin part of the oxyhæmoglobin molecule which holds the oxygen, and the power the hæmatin has of combining with the oxygen seems to depend upon the amount of iron present in it. The formula for hæmatin is $C_{32}H_{32}N_4O_4Fe$ (*vide* p. 254). The oxygen, combined with the hæmoglobin, as oxyhæmoglobin in the erythrocytes, is carried back from the lungs to the left side of the heart, and by it is driven to the tissues. It is calculated that arterial blood is only nine-tenths saturated with oxygen, and that, in ordinary circumstances, only about one-third of the combined oxygen is used. In emergencies, therefore, there is a considerable proportion of oxygen to draw upon; in other words, arterial blood, in ordinary circumstances, contains much more oxygen than the tissues immediately need.

2. **Carbon-dioxide.**—The carbon-dioxide which is produced in the tissues returns to the lungs in the venous blood. One hundred c.c. of venous blood contain about 46 c.c. of carbon-dioxide; of this amount 95 per cent. is in combination, and only 5 per cent. in simple solution in the plasma. Now, the larger proportion of the carbon-dioxide which is combined appears to be *adsorbed* to the proteins of the blood, some of the carbon-dioxide is held by the serum globulin, and some by the hæmoglobin of the erythrocytes. It is the histone globin of the hæmoglobin which adsorbs the carbon-dioxide, and as the hæmatin part of the oxyhæmoglobin has been

robbed of its oxygen by the tissues, so the globin is increasingly capable of adsorbing carbon-dioxide. A smaller proportion of the carbon-dioxide which is in the blood is chemically combined with the sodium salts as sodium bicarbonate, and a very small proportion is present as sodium carbonate. It will be seen, then, that the CO_2 in the venous blood, pumped by the right ventricle to the lungs, is present, adsorbed to the hæmoglobin and to the serum globulin, also chemically combined as $NaHCO_3$ (much) and Na_2CO_3 (little). It is possible, too, that some is present in simple solution. Carbon-dioxide is much more soluble in water than oxygen is.

CO_2 leaves the venous blood in the pulmonary capillaries and gets into the alveolar air, where its tension is usually 5 per cent. in males, and 4·7 per cent. in women and children. The tension of carbon-dioxide in venous blood is higher than 5 per cent.; in the dog it has been estimated at 5·4 per cent.; so that it is by diffusion that the CO_2 leaves the venous blood and enters the air in the alveoli, and it is by a continuation of the process of diffusion that the CO_2 leaves the air in the alveoli and enters the bronchioles. It may be asked, what causes the CO_2 to leave the hæmoglobin and to go into solution in the plasma? It may be that, as the oxygen gets into the plasma, the hæmoglobin takes it up, and in proportion as it combines with the O so it sets free the CO_2, which consequently causes the CO_2 tension in the plasma to rise. The flattened cubical cells lining the alveoli prevent the CO_2 from diffusing from the alveoli, where its tension is 5 per cent. (in man), back to the plasma of the arterial blood, where the tension of the CO_2 is only 2·8 per cent.

RESPIRATORY CHANGES IN THE TISSUES, OR TISSUE RESPIRATION.

These changes are sometimes known as internal respiration, and include the gaseous interchange between the blood, the tissue fluid or lymph, and the cells of the tissues themselves. The oxyhæmoglobin which is carried to the tissues is nearly completely saturated with oxygen, although the oxygen is only loosely combined with the hæmoglobin. Living tissues have a great affinity for oxygen, which they take from the oxyhæmoglobin. The tissues can reduce methylene-blue, which is a much more stable compound than oxyhæmoglobin.

Ehrlich first demonstrated this as follows:—A solution of methylene-blue was injected into the vein of a living animal, and after a short time the animal was killed. The blood was found to be coloured with the methylene-blue, but the muscles retained their normal colour. On exposing the muscles to oxygen, they became blue; thus showing that during life the muscles were capable of taking oxygen from a stable compound like methylene-blue; but the deoxidised methylene-blue which was in the tissues was reoxidised, and again becomes blue when the tissues were exposed to free oxygen. The oxygen tension of the tissues is nil, which indicates that the oxygen present is intimately adsorbed or chemically combined. At any rate, it is stored in some way or other, for it is *not* used for oxidisation immediately it arrives in the tissue cells. The tissues control their own respiration, and even if an excess of oxygen were supplied to the tissues they would not necessarily utilise it. The oxygen which has been adsorbed in the tissues is *eventually* used to oxidise the already adsorbed carbohydrate, fat, and, in some circumstances, the protein. The carbon is oxidised to CO_2, and the hydrogen to form H_2O. Some of the oxygen is used, however, to oxidise other bodies, and to form such substances as urea, xanthine, and uric acid. This change may be brought about by tissue enzymes, called oxidases. As the CO_2 is produced in the tissues so its tension rises, and it consequently diffuses from the tissues into the tissue lymph, where some of it passes, via the lymph stream, into the venous blood. The larger quantity, however, leaves the tissue lymph and passes into the plasma, whence it returns to the lungs. As has been previously stated, some of the CO_2 is adsorbed to the proteins in the blood, and some is combined chemically as $NaHCO_3$ and Na_2CO_3.

The gaseous interchange between the blood and the tissues indicates the metabolic changes which occur in the tissues, and the work done by the tissues can be approximately estimated by obtaining the following data:—

1. Estimating the O and CO_2 in the arterial blood going to an organ, and in the venous blood leaving the organ. This is most readily done by Barcroft's method (*vide* p. 335).
2. Estimating the volume of blood passing through the organ in a given time.

3. After the animal is killed the organ should be weighed, so that the gaseous exchange per grm. can be calculated.

As a result of such experiments it has been shown that, during increased tissue activity there is an accelerated blood flow and an increased gaseous interchange in the organs, indicating increased metabolism. If the nerves to a part are cut the gaseous exchange is decreased and the blood flow also decreased; this indicates diminished metabolism. Moreover, it has been shown that the *ratio* of the CO_2 produced to the O used up remains the same, whether the nerves to the part are intact or divided.

CHAPTER XXVI.

INFLUENCE OF RESPIRATION UPON THE CIRCULATION.

The blood pressure in the pulmonary artery is 25 mm. Hg, whereas that in the carotid artery is 140 mm. Hg. Vasomotor nerves to the lungs run in the third, fourth, and fifth dorsal nerves; these are distributed to the bronchial arteries. It is generally believed that the pulmonary arterioles are not controlled by vasomotor nerves; adrenalin, which acts upon the terminations of these nerves, has no action upon the pulmonary arterioles. It will be understood, then, that adrenalin is useful in hæmorrhage from a bronchus or bronchiole, due to ulceration into a bronchial artery or arteriole, but that it is quite useless in hæmorrhage from the lung tissue itself; in fact, it can only do harm by raising the general arterial blood pressure and causing increased congestion of the pulmonary tissue.

Respiration influences the circulation in three ways:

1. Mechanically.
2. Reflexly.
3. Chemically.

1. **The Mechanical Effect.**—It has been pointed out that the pulmonary vessels are not controlled by vasomotor nerves, but it may be that their place is taken by the vagi which control the tonus of the bronchiole muscles, and therefore, by regulating the tension of the air in the infundibula, allow the thoracic movements to act mechanically upon the lung capillaries. The variations of intrathoracic pressure, produced by the respiratory movements of the thorax, have practically no influence upon the thick-walled arteries contained therein, or upon the walls of the ventricles; but the veins, with their thinner walls, and the auricles are undoubtedly influenced. The elastic tissue contained in the lungs is always somewhat

stretched, even at the end of expiration; it therefore tends to retract, but much more so at the end of inspiration. The lungs, therefore, always exert a pull upon the thorax wall. If a mercurial manometer is connected with the pleural cavity, at the end of expiration it registers a pressure of -6 mm. Hg. During inspiration the negative pressure in the pleural cavity must obviously become more negative in proportion as the elastic tissue in the lungs is further put on the stretch, so that at the end of deep inspiration a pressure of -30 mm. Hg may be registered. The veins and the auricles must be influenced by such a distinct change of pressure occurring throughout the inspiratory movements. The thorax exerts a distinct aspiratory influence upon the blood flow in the veins, which means that during inspiration not only air, but also venous blood, is drawn into the thorax. The venous blood pressure in the extrathoracic veins is lowered during inspiration, because the blood is drawn into the somewhat distended thoracic veins from the head and neck, the arms, the leg, and the abdomen. At the same time, the venous blood is more readily drawn into the right auricle, which also distends more easily during inspiration. If the thorax is so compressed, as may sometimes happen to individuals in a crowd, its aspiratory influence can no longer be exerted, the circulation begins to fail, and death may ensue. The effect of expiration is to diminish the negative intrathoracic pressure, the right auricle becomes distended less readily, the venous blood flows less easily into the thorax, and the extrathoracic venous blood pressure becomes consequently raised. In persons suffering from chronic bronchitis and emphysema, a condition in which the tissue of the lungs becomes less elastic, there is consequently produced an impediment to the pulmonary circulation; prolonged expiratory blasts, such as coughing, may so raise the venous blood pressure that the systemic capillaries become engorged and may eventually rupture; this is seen in the epistaxis, or nose bleeding, which frequently ensues.

Respiratory movements have the opposite effect upon the arterial blood pressure to that exerted upon the venous blood pressure. During inspiration venous blood is drawn into the right auricle, thence to the right ventricle, and so finally driven to the lungs. Just as inspiration aids the distension of the right auricle, and accommodates the venous blood entering the thorax, so inspiration causes the left auricle to become more readily distended, and thus induces the blood to leave the lungs in the pulmonary veins; this blood is readily poured into the left auricle. The result of the distension of the left auricle is that the left ventricle is supplied with more blood, which it promptly dispatches to the arteries; in other words, the effect of inspiration is to *raise* the arterial blood pressure. The effect of expiration, which increases the resistance to the blood flow through the lungs, is to cause a slight *fall* in arterial blood pressure.

If an arterial blood pressure tracing is carefully examined,

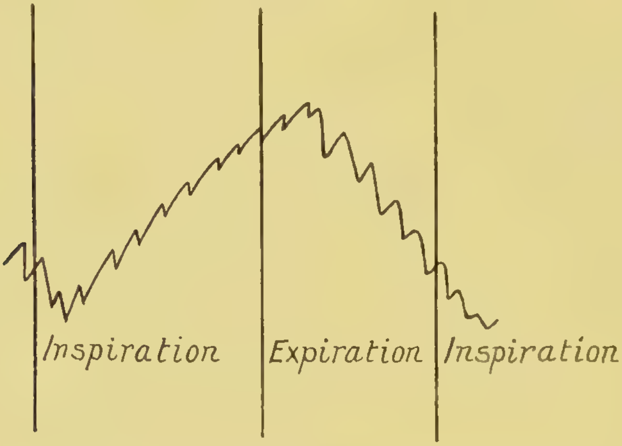


FIG. 51.—The diagram represents the relationship of respiratory movements to the blood pressure. The arterial blood pressure rises during inspiration, and continues to rise in the early stage of expiration. As expiration continues the arterial blood pressure gradually falls, and continues to fall during the early stage of inspiration.

it will be seen that the arterial blood pressure continues to fall during the earliest stage of inspiration, and to rise during the earliest stage of expiration. This is accounted for by the mechanical effect of the respiratory movements upon the capillaries of the lungs. During inspiration, if the tonus of the bronchiole muscle is maintained, the tension of the air in the infundibula is so regulated that there is some distension of the lung capillaries in the walls of the alveoli; that is, with the ordinary distension of the lungs during inspiration the capillaries are capable of holding more venous blood to be rendered arterial. It has been estimated that, at the height of inspiration, the lungs are capable of holding one-twelfth of the whole blood of the body, and during expiration the amount diminishes to one-eighteenth of the total blood volume. In the early stage of inspiration, therefore, the venous blood which enters the lungs is used in filling the distending lung capillaries, pools there, and does not go on at once to the pulmonary vein; hence the arterial blood pressure continues to fall for a very short period. During expiration, however, the capacity of the lung capillaries for holding blood diminishes, with the result that the blood is squeezed out into the pulmonary veins, thence to the left auricle and ventricle; consequently the arterial blood pressure continues to rise during the early stage of expiration.

2. **The Reflex Effect of the Lungs upon the Heart.**—During the gradual distension of the infundibula during inspiration, impulses arise in the walls of the alveoli which travel by the vagi to the cardiac centres in the flow of the fourth ventricle, the result of which is that the heart beats more quickly. When the infundibula undergo partial collapse during expiration, impulses similarly arise in the walls of the alveoli, which travel viâ the vagi to the cardio-inhibitory centres which increases their activity, with the result that the heart beats more slowly. Great distension of the alveoli, as may be caused by forcible positive ventilation, faradising the upper (central) cut end of the vagus, or by blowing chloroform vapour, or bromine water, down the trachea, usually causes reflex inhibition of the heart. It will be noted, then, that the heart beats more quickly during inspiration and more slowly during expiration, but these differences of heart beat disappear after both vagi are cut, the consequence of which is that the afferent impulses from the infundibula to the brain are prevented.

3. **Chemical Influence.**—The result of the act of respiration is that the hæmoglobin becomes very nearly saturated with respiratory oxygen, some of which, of course, is carried to and supplied to the nerve cells of the vasomotor centre, and upon this depends, to a very considerable extent, the tonic activity of the vaso-constrictor part of the vasomotor centre. If, however, the oxygen tension of the blood is diminished, and the carbon-dioxide tension raised, such as occurs in asphyxia, the vaso-constrictor centre becomes more irritable and the arterial blood pressure rises somewhat; this is shortly followed

by a very considerable fall, as the vasomotor centre becomes exhausted.

ASPHYXIA.

The phenomena which occur, when the supply of oxygen to the respiratory centre is diminished, and the tension of carbon-dioxide in the blood unduly rises, are known as asphyxia.

These changes may be brought about experimentally by one of the following methods :—

1. Plugging, tying, or clamping the trachea.
2. Producing double pneumo-thorax, a condition in which the lungs collapse through the influence of the elastic tissue which they contain.
3. Cutting off the arterial blood supply to the brain by tying both common carotid and both vertebral arteries.
4. By prolonged bleeding, which causes anæmia of the blood.
5. Making the animal breathe a gas devoid of oxygen.

The phenomena of asphyxia may be divided into the following four chief stages :

1. Increasing dyspnœa.
2. Expiratory convulsions.
3. Exhaustion.
4. Inspiratory spasm.

1. **Stage of Increasing Dyspnœa.**—After the trachea has been tied, the former normal breathing (eupnœa) is replaced by excessive respiratory movements, or hyperpnœa, which is the early stage of dyspnœa (difficulty of breathing), and for the next two minutes the dyspnœa gradually deepens. During this period there is an increased rhythm of the respiratory movements, probably due to afferent impulses from the lung infundibula via the vagi. At the same time there is an increased amplitude or depth of the inspiratory efforts due to the increased irritability of the respiratory centre, brought about by the increased CO_2 tension in the blood stream. At first there is an exaggerated effort on the part of the inspiratory muscles, which soon gives place to an exaggerated effort on the part of the expiratory muscles. During this period the arterial blood pressure gradually rises,

due to the increasing venosity of the blood, which stimulates the vaso-constrictor part of the vasomotor centre to increased activity. At the same time, the venous blood may act locally upon the peripheral arterioles, increasing their muscular tone. Occasionally a slight fall in arterial blood pressure occurs before the early rise; this may be due to a certain amount of shock which is produced by the operation of tying the trachea. With this increased resistance to the circulation the heart beats more forcibly and more frequently. The mucous membranes of the animal become somewhat cyanosed (blue), and the pupils become equally contracted.

2. **Stage of Expiratory Convulsions.**—During this stage, which lasts about one minute, the expiratory efforts are violent and convulsive. The raised CO_2 tension of the blood increases the irritability of the nerve cells of the brain and spinal cord, with the result that the convulsive seizures become more or less general. If the animal is not already anæsthetised, unconsciousness at this stage supervenes. The arterial blood pressure gradually falls, due to exhaustion of the vasomotor centre, but with each convulsion there is a rise of arterial blood pressure. The heart beats less forcibly, due chiefly to exhaustion.

3. **Stage of Exhaustion.**—The animal at this stage lies quite quiet, as a rule, making no attempt whatever at respiratory movements. The arterial blood pressure gradually falls, and, on the blood pressure tracing, respiratory movements are absent; heart beats are still seen, though these are extremely feeble. This stage lasts about three minutes, the pupils of the animal become equally widely dilated, and the eyeballs somewhat prominent. On the blood pressure tracing, which now shows a rapid fall in pressure, may be seen two or three long-drawn-out curves, during which the arterial blood pressure rises slightly, only, however, to fall again. These are Traube-Hering curves, and are due to efferent impulses from the vaso-constrictor centre which travel down the spinal cord to the peripheral arterioles, with the object of producing vaso-constriction, raising arterial tone, and of restoring the failing circulation.

4. **Stage of Inspiratory Spasm.**—The animal may make one or two inspiratory efforts before it finally stretches itself out and dies.

Post-mortem Findings in Death from Asphyxia.

If the asphyxia has been caused by tying the trachea, on immediate post-mortem examination the large veins will be full of venous blood, the right auricle distended, the muscle of its wall contracts rhythmically; the right ventricle is also distended, and the pulmonary artery is full of blood. The lung infundibula are over-distended, causing the lungs to be emphysematous and pink in colour. The pulmonary vein is almost empty, the left auricle and left ventricle are comparatively empty, and the arteries contain very little blood. The impediment to the circulation seems to be in the lungs, causing the blood to accumulate on the venous side of the circulation, whereby the arterial side of the circulation becomes comparatively empty.

THE EFFECT OF ALTERATIONS OF ATMOSPHERIC PRESSURE.

The atmosphere consists of nitrogen 4 parts and oxygen 1 part; that is, the normal O pressure is one-fifth of an atmosphere. The atmospheric pressure stands at 760 mm. Hg, so that the normal oxygen pressure is one-fifth of 760 mm. Hg = 152 mm. Hg. As respiratory oxygen is chemically combined with the hæmoglobin, slight variations of oxygen pressure are compatible with normal respiration.

Well-defined Variations of Oxygen Pressure.

1. **Increased Oxygen Pressure.**—It is found, if the sartorius muscle or the heart of the frog is exposed to eighty atmospheres of O for from a half to two hours, it becomes paralysed. If a toad is exposed to twenty atmospheres of O for forty minutes, and then decompression brought about, convulsions occur and death takes place. On post-mortem examination, gas bubbles are found in the lymph spaces of the body, in the aqueous chamber, and also in the cavities of the heart. Caisson workers are exposed to compressed air, but it is dangerous for them to work in an atmosphere in which the O pressure is greater than four atmospheres of O. Decompression ought to take place very gradually, about twenty minutes being allowed for each atmosphere. If decompression takes place too rapidly, vertigo with deafness and paralysis occurs. These

conditions are, in all probability, due to the liberation of free nitrogen which has been absorbed by the plasma under the increased pressure. This nitrogen is found in the lymph spaces and capillaries, and particularly in the grey matter of the spinal cord and the internal ear. It is to the nitrogen blocking the capillaries of the grey matter of the brain and spinal cord that the symptoms of caisson disease are due.

Haldane has shown that animals can live in two atmospheres of O after all the hæmoglobin is combined with CO as carboxyhæmoglobin. In these circumstances the O is dissolved in the plasma. In coal gas poisoning the blood contains carboxyhæmoglobin. The condition should be treated by performing artificial respiration, and then causing the patient to breathe O under pressure. Ten to twelve ounces of blood should then be withdrawn from the median basilic vein, and a corresponding amount of warm isotonic salt solution allowed to run into the vein.

2. **Diminished Oxygen Pressure.** — Mountain climbers, balloonists, and aeroplanists are exposed to a diminished O pressure. Those who habitually live at high altitudes develop an increased number of erythrocytes in order to carry the requisite amount of O to the tissues.

At the height of Mont Blanc, *i.e.* 4800 metres above the sea level, the atmospheric pressure is 418 mm. Hg. Since the normal oxygen pressure is 20 per cent. of an atmosphere, oxygen pressure, when the total atmospheric pressure is 418 mm. Hg, is only about 11 per cent. Under this diminished O pressure mountain sickness frequently supervenes, and death may occur from the reduced O tension; this can be prevented, however, by causing the patient to breathe O under pressure from a gas cylinder.

SECTION VIII.

METABOLISM.

CHAPTER XXVII.

THE METABOLISM OF PROTEIN.

FROM a chemical standpoint the composition of the body may be expressed as "proteins, fats, carbohydrates, salts, and water," but such a mixture, even in the exact proportions in which it occurs in the different tissues of the body, would not perform the functions of life. Life and its phenomena depend upon deep-seated chemical reactions occurring in these various substances, which never cease during the life of the animal. These changes are expressed by the term "Metabolism." Metabolism is a comprehensive term which includes all the chemical changes which are constantly taking place within the body during its lifetime. In the case of food stuffs it includes all the changes which these undergo from the moment of their absorption until they are finally voided, in an altered form, as excretions. Similarly, the oxidative processes must likewise be regarded as forming part of metabolism.

Metabolism, as it goes on in the body, fulfils two purposes :

1. The maintenance of the substances unimpaired which constitute the various tissues.

2. The conservation of the energy of the body, and the production of animal heat.

Considered in a general way, the metabolic processes may be divided into two classes,—those of **anabolism** and those of **katabolism**, or changes of a constructive and disruptive character respectively. The katabolic processes are those processes necessary for the production of the energy manifested by the animal body. They involve the conversion of the complex constituents of the animal body into the simpler substances found in the excretions. Such changes involve hydrolysis, oxidation, and possibly reduction. By these processes the potential energy, stored up in the complex materials as chemical energy, is liberated, and utilised by the organism in the performance of work, for the production of heat, etc. Such changes obviously demand reparation in order that the organism may not undergo disintegration. Such reparative processes are provided in the processes of anabolism. Anabolic changes are those involving construction, the formation of the complex materials of the tissues from the simpler materials presented for such repair.

Observations on metabolism in certain diseases, and in animals, as the result of experiment, have yielded up one or two links in the great chain of metabolic events, but so far most of the other links have had to be filled in by means of hypotheses, and yet await experimental confirmation. At the same time signs are not lacking that, in the future, the events of the metabolic cycle will be ascertained by the investigator.

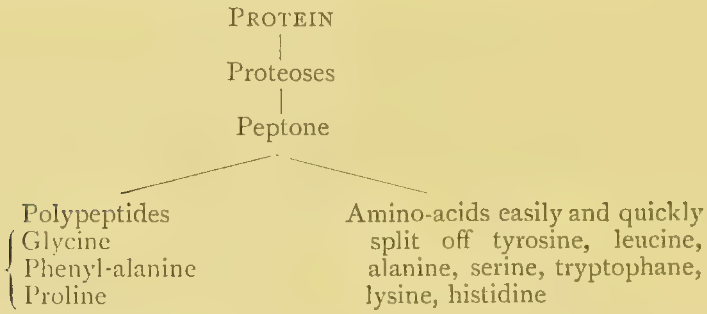
PROTEIN METABOLISM.

A. Anabolism.

Protein in Food.—Under normal conditions food consists of a mixture of proteins, fats, carbohydrates, salts, and water. The amounts of these different materials vary with the different dietaries, a point to be referred to later, but here it may be said that, in normal circumstances, the amount of protein daily ingested is about 100 grms. (*vide* p. 73). With regard to the different food stuffs enumerated above, three only are an absolute necessity for the maintenance of life,—protein, water, and salts. A diet consisting of these materials only will suffice, but one in which protein is absent is of no avail. This will be readily understood when it is remembered that, according to present knowledge, animals are unable to synthesise complex organic materials from simple inorganic substances, and the statement that protein food stuff is an absolute essential for the prolongation of life must be interpreted as meaning that, unless an animal is provided with either protein or protein derivatives, it is unable to build up again the protein, which has been katabolised, in order to yield the energy necessary for the performance of the phenomena of life.

The Absorption of Proteins.—As a result of researches carried out by Fischer, Kossel, and others, it is now evident that proteins are long chains of a number of nitrogenous derivatives of lower fatty acids, many of which contain an aromatic group. In the intestines, as a result of the combined action of the different enzymes—pepsin, trypsin, and erepsin—these chains are probably almost completely broken down, with the production of free amino-acids and certain short chains of amino-acids called polypeptides. Those amino-acids set free are leucine, tyrosine, alanine, histidine, lysine, valine, tryptophane, serine, cystine. Those which are not set free, but remain in a polypeptide form, are glycine, phenyl-alanine and proline (Abderhalden). These bodies are then absorbed by the columnar epithelial cells covering the villi of the small intestine.

Significance of Polypeptides formed during Digestion.—The products formed during digestion from protein material may accordingly be shown thus :—


PROTEIN
Proteoses
Peptone
Polypeptides
Glycine
Phenyl-alanine
Proline
Amino-acids easily and quickly split off tyrosine, leucine, alanine, serine, tryptophane, lysine, histidine

These polypeptide bodies so formed appear to be of great importance in the further history of the protein food material. Loewy found that a dog was able to maintain itself in good condition upon a diet consisting of the cleavage products of protein produced by tryptic digestion. At the same time, while this is undoubtedly the case, other observers (Henriques and Hansen) have shown that, if the crystalline products of protein hydrolysis, produced by boiling with a mineral acid, are given to an animal, that animal very soon dies, being unable to maintain itself in good condition upon the food supply given. It seems, therefore, that in an "enzyme digest" something is present which is absent from an "acid digest" of protein material; and since it is known that acid effects a complete hydrolysis, it appears that it is the polypeptides left in "tryptic digests" which are so necessary for the further building up of protein material in the animal body. In fact, as Abderhalden suggests, it seems as if this polypeptide were purposely left in tryptic digestion in order to form a foundation stone upon which proteins can be built up.

Purpose of Digestion.—It would seem at first sight as if the cleavage of proteins effected in the alimentary canal were an unnecessary process, and that the absorption of proteins would be effected equally well if the cleavage were only effected as far as the peptone stage. The great function of digestion, however, is not merely to affect an absorption of food material (there is evidence, in fact, that albumin itself is absorbed in an unaltered condition when given per rectum), but to so alter all those different foreign proteins, given by the mouth, that they ultimately come to yield the same simpler bodies, namely, the amino-acids. That is to say, the purpose of digestion is to cause the resolution of myosin (of muscle) edestin (of the Brazil nut), casein (of curdled milk), gliadin (of wheat), etc., into those bodies common to all, namely, the amino-acids. In this way the body always has a constant supply of material presented for absorption.

Form of the Absorbed Protein in the Blood.—The further history of the cleavage products, after their absorption by the epithelial cells of the villi, has led to considerable discussion. At the present time two views are held.

1. According to one, the amino-acids are passed on into the blood of the portal capillaries as such by the epithelial cells, and as such gain access to the individual cells of the body. Support is furnished to such a view by the fact that certain amino-acids have been discovered in the blood (Howell, Leathes). It is not negatived by the fact that the amounts found are very small; for Abderhalden has shown that, even when large amounts of a single amino-acid are injected into the blood, after the lapse of a very short time it cannot be detected. Further, the portal blood passes immediately to the liver, and this organ utilises very quickly those amino-acids which are contained in the blood. This is a plausible view, as it brings the different amino-acids into close relation-

ship with the different tissues, so that these are enabled to conveniently take up any particular amino-acid that they may be in need of at the moment.

2. The other and older view has the support of many physiologists. It maintains that, in the intestinal epithelium, the amino-acids are built up again into those proteins, serum globulin and serum albumin, which are present in the blood. In this way the different tissue elements have presented to them a food material of a constant and almost invariable composition. In fact, Abderhalden maintains that this uniformity of food supply is one of the most important factors in the maintenance of the individuality of the species. The invariability of this composition, if indeed the blood proteins are so built up, is strikingly manifested in an investigation carried out by Abderhalden and Samuely. These investigators bled a fasting horse until the amount of its circulating blood proteins was greatly reduced. They estimated the amount of the different amino-acids contained in the blood proteins thus obtained. Then they fed the animal upon gliadin, the protein of wheat, which contains about five times as much glutamic acid as the blood proteins, and they again estimated the content of the blood proteins. It was found that the regenerated blood proteins contained precisely the same content of individual amino-acids as did the blood proteins at the beginning of the experiment. This fact, however, does not stand in any way in conflict with the view that the blood proteins are formed in the intestinal epithelium from the individual amino-acids, it merely emphasises the important part which these cells must play in remodelling the ingested proteins. The important part which cells may take in the alteration of absorbed materials is well emphasised by an experiment of Abderhalden and Rona. They fed the mould *Aspergillus niger* upon the most diverse nutritive media, but they could not find any alteration in the chemical constitution of that organism.

The further History of the Absorbed Protein.—The further history of the absorbed protein material is intimately bound up with the other side of protein metabolism, namely, katabolism. Since protein forms, according to present conceptions, the living material of the different tissues of the body, it follows that activity of any, or all, of the tissues of the body is bound to lead to disintegration and decomposition of some at least of the proteins constituting this active tissue.

On the other hand, it is obvious that the tissues may be able to utilise energy, which is set free by the decomposition of that protein, which has not formed part of its own constituent protoplasm. It is very probable, however, that the major part of the energy evolved must throw some strain upon, and cause some destruction of, the constituents of the living tissues. The further history of the protein food is intimately bound up with this question, and at present three different views are put forward.

1. According to *Pflüger*, the energy manifested in all the different processes of life is derived from the oxidation of the actual material of the living cells. He assumed that all the absorbed protein is built up into the living material (anabolism) before it undergoes the changes of katabolism.

2. According to the theory of *Voit*, the protein of the tissues, "living" or "organised protein," is to be differentiated from the absorbed "circulating protein." It is only in this "circulating protein," which is assumed to be present in the fluids of the body, the blood and lymph, that katabolic changes take place. These changes take place under the influence of the living cells. The more resistant "organised protein" is not supposed to undergo katabolic changes. If any of it does, it is cast off into the fluids of the body, and thus becomes "circulating protein," undergoing katabolic changes in precisely the same manner. It is obvious that a small part of the absorbed protein must be utilised to replace the waste of the "organised protein" and to subserve the process of growth. This portion is termed "tissue protein."

3. *Folin's View.*—This theory is of recent origin, and assumes that neither of the views given above is correct. It maintains that there are two kinds of protein metabolism in the body, *endogenous* and *exogenous.* Endogenous is the metabolism of the tissues, and represents the destruction of tissue necessary for the normal maintenance of the bodily functions. Obviously, then, it is constant, and is independent of the amount of food taken. Further, its amount represents the least amount of protein necessary for the maintenance of life, for it is clear that life can be maintained so long as this necessary expenditure is replaced. On the other hand, exogenous protein metabolism is larger in amount, it is inconstant, and it varies with the amount of protein material ingested. It is probable that the energy derived from this

metabolism might be easily replaced by the utilisation of non-nitrogenous materials—fats and carbohydrates—without any untoward results. This is very evident when a further aspect of the theory is considered. It is believed that the protein necessary to replace the endogenous metabolism is either built up from amino-acids by the columnar cells over the villi, or in the tissues themselves. All the other amino-acids not so utilised are, so it is believed, carried to the liver, where they undergo the first stage of exogenous metabolism. That is to say, they are deamidised, their nitrogen being split off as ammonia, and utilised in the formation of urea. The carbon chains so left are utilised in precisely the same manner as carbohydrates and fats are. It is even possible that the carbon may be utilised in the formation of these substances.

Synthesis of Proteins from Material other than Protein or Protein Products.—It is obvious, since the animal organism can utilise nitrogen only when it is presented in the form of protein, that in the animal body a synthesis of protein material from material other than protein, such as fats and carbohydrates, is an impossibility.

B. Katabolism.

It is obvious, *a priori*, if when large amounts of protein food are ingested and the adult animal does not increase in size proportionally, that this food must in some way be destroyed, or utilised in some way or other to replace proteins of the tissues which have been previously destroyed. As a matter of fact, both processes occur, one part replacing the protein destroyed in the changes of endogenous metabolism (Voit's "tissue protein"), and the remainder itself undergoing exogenous metabolism. It is natural, therefore, to examine the various excreta with a view of determining bodies formed as a result of this destruction. From the chemical standpoint, as has already been shown, proteins consist of long chains of amino-acids (glycine, alanine, serine, valine, leucine, lysine, arginine), which in some cases are benzoylated (tyrosine, phenylalanine), or contain heterocyclic bodies (tryptophane, proline, oxyproline, histidine), and others again contain sulphur (cystine, cysteine). Certain conjugated proteins also contain phosphorus. It is obvious, then, that the products of protein metabolism should be recognised in the various excreta. On examining the excreta with this object, it is found that derivatives containing nitrogen, sulphur, phosphorus, cyclic, and heterocyclic rings are found in the urine; further, that similar bodies exist in the fæces, and that in the sweat also nitrogenous bodies are sometimes present. Again, since on calculation it is found that all the carbon and hydrogen, corresponding with the protein decomposed (calculated on the amount of nitrogen eliminated) is not eliminated in combination with the nitrogen of the excreta, it is reasonable to presume that the excess of these elements is got rid of as carbon-dioxide and water by the urine, the lungs, and the skin.

Returning again to the subdivision of protein metabolism into endogenous and exogenous portions, it is evident that, in order to determine the excretory products due to one or the other of these katabolic processes, it is necessary only to starve the animal. In these circumstances, such products as are formed are due entirely to katabolic endogenous metabolism.

The Intermediate Products of Metabolism.—There is every evidence that, in the formation of those metabolic end products, which are under consideration, an intermediate stage is the resolution of the protein into its constituent amino-acids. This conclusion is supported by the following observations:—

1. In abnormal conditions, such as acute yellow atrophy of the liver, and especially in conditions involving diminution of the oxidative processes, such as occur in phosphorus poisoning, certain of the amino-acids (leucine and tyrosine especially) are found in the urine.

2. The facts of autolysis furnish support to this view. By autolysis or "self-digestion" is meant that an isolated organ, if kept in sterile conditions, undergoes liquefaction, and becomes resolved into its various amino-acids and ammonia. This change is due to the activity of its intracellular enzymes, which evidently become active immediately after death. Although there is no reason to suppose that such a sweeping change as this is a normal occurrence within the confines of the animal body, yet there is every reason to think that the changes which do occur in the body are of a precisely similar nature, except that the activities of the different enzymes are carefully kept under control.

THE END PRODUCTS OF PROTEIN METABOLISM.

Urea.

Occurrence of Urea.—This is one of the most important end products of protein metabolism. It is in this form that the greater part of the nitrogen of the protein molecule is excreted. It is eliminated almost entirely by the urine, being found in it in the considerable concentration of 2 per cent. The daily excretion averages 35 grms. A very small portion also is excreted by the sweat, but, in normal circumstances, the amount so got rid of is negligible, although the quantity so lost may be increased by hard work.

The Formation of Urea.—Urea is derived from protein, and the points to determine are—

1. Where it is formed; and
2. What its immediate precursors are.

With regard to the former, it was once thought that urea was produced in the kidney. This, however, was shown not to be the case by the following experiments:—

1. When defibrinated blood is irrigated through an isolated kidney, it contains those bodies from which an immediate formation of urea might be expected (ammonium carbonate, etc.), while no increase in the amount of urea in the circulated blood is found.

2. When both kidneys are removed, and the animal is kept alive as long as possible, it is found that the urea in the blood increases, and steadily accumulates as long as the animal remains alive.

Repeated research has shown that it is the *liver* which plays the chief part in urea formation. The following experiments demonstrate this fact:—

1. If the liver of a frog is extirpated it is found that the excretion of urea almost ceases, and that ammonia is found in its place.

2. Mammals do not tolerate this operation, but die almost immediately. The liver can be put out of the general circulation, however, by means of an "Eck's fistula." That is to say, an artificial anastomosis is established between the portal vein and the inferior vena cava, the organ receiving blood from the hepatic artery only. The animals may in this way be kept alive for some time, and it is found that the amount

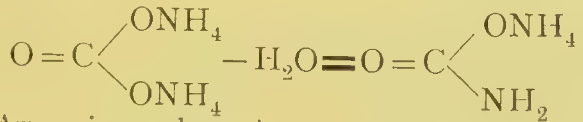
of urea in the urine diminishes, while at the same time the output of ammonia increases. After a time, however, the animals exhibit symptoms of poisoning (Ammonæmia). This experiment is often verified in disease. In acute yellow atrophy of the liver, and also in atrophic cirrhosis of the liver, the liver cells undergo degeneration and destruction, and for functional purposes are as little useful as if an "Eck's fistula" had been established. In these conditions it is found that the amount of urea excreted in the urine has diminished, but that the amount of ammonia has increased. At the same time, there are considerable amounts of amino-acids (leucine and tyrosine) in the urine.

It is obvious, then, from these experiments, that the principal place of formation of urea is the liver, and that from this organ it is carried to the kidneys, where it is finally excreted.

It is quite possible, however, that in the case of acute yellow atrophy of the liver the leucine, tyrosine, and ammonia which appear in the urine, are partly derived from the tissue proteins of the liver cells, which have been destroyed as the result of the poisons which attack them.

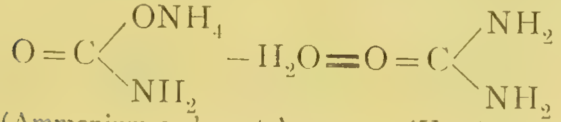
Precursors of Urea.—

1. Urea is formed in the Liver from Ammonium Compounds.—Thus if ammonium carbonate is perfused through the liver of an animal, urea is formed (Schröder); similarly, ammonium carbamate also yields urea (Nencki). The formulæ of these substances and their relationship to urea are thus indicated:—



$$O{=}C\left<\begin{matrix}ONH_4\\ \\ ONH_4\end{matrix}\right. - H_2O = O{=}C\left<\begin{matrix}ONH_4\\ \\ NH_2\end{matrix}\right.$$

(Ammonium carbonate) (Ammonium carbamate)



$$O{=}C\left<\begin{matrix}ONH_4\\ \\ NH_2\end{matrix}\right. - H_2O = O{=}C\left<\begin{matrix}NH_2\\ \\ NH_2\end{matrix}\right.$$

(Ammonium carbamate) (Urea)

The change is one of dehydration.

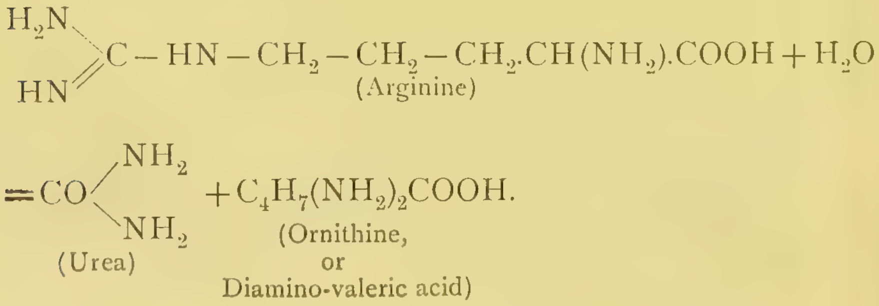
This supposition is further confirmed by the fact that Nencki, Pawlow, and Zaleski have found that the percentage of ammonia in the portal blood is three or four times greater than that in the general circulation. After an "Eck's fistula" is established it is found that the percentage of ammonia in the blood is everywhere the same.

The ammonia in this case arises from the products of the digestion of protein in the alimentary canal. The results of proteoclastic changes in the intestine are the production of ammonia and the amino-acids. It is this ammonia which is found in the portal vein, and which thus plays such a share in the formation of urea.

At the same time, however, it is probable that ammonia arises also in the other tissues. This supposition is supported by the fact that the content of ammonia in the tissues is greater than that in the blood. Further, Lang has shown that in the tissues there are intracellular enzymes capable of splitting off ammonia from the different amino-acids, and, even if any tissue protein underwent hydrolysis, a certain amount of ammonia would be set free.

2. Urea is produced also from the Mono-amino Acids.—If glycine, alanine, leucine, aspartic acid, etc., are given to an animal by the mouth, or injected subcutaneously, there is an increase in the amount of urea excreted. This change takes place in the liver, for it has been shown that, if these monoamino acids are circulated through the liver, urea is formed from them. It seems that, in the liver itself, they suffer deamidisation, and the free ammonia is at once transformed into urea. The carbon chains thus freed may either be converted into CO_2 and H_2O, with the resulting production of energy, or be transformed into carbohydrates and fats.

3. With regard to the Diamino Acids, the production of a certain amount of urea is a very simple matter. Drechsel some years ago found that one of them, arginine, yielded urea upon simple hydrolysis with baryta water. This change is represented thus—



Within recent years Kossel and Dakin have shown the presence of an enzyme—arginase—in certain of the tissues, especially the liver, capable of effecting this change. The amount of urea thus formed from the tissue proteins (endogenous), has been estimated at 5 per cent. of the total excreted.

W. H. Thompson has also made the interesting observation that, if arginine is fed to an animal, there is an immediate increase in the urea excretion, due to the urea split off from the arginine molecule, succeeded later by an increase due to urea from the ornithine fraction.

4. A FOURTH SOURCE OF UREA IS PROVIDED IN THE ENZYMATIC DESTRUCTION OF URIC ACID.—This will be discussed later on under the heading of Uric Acid.

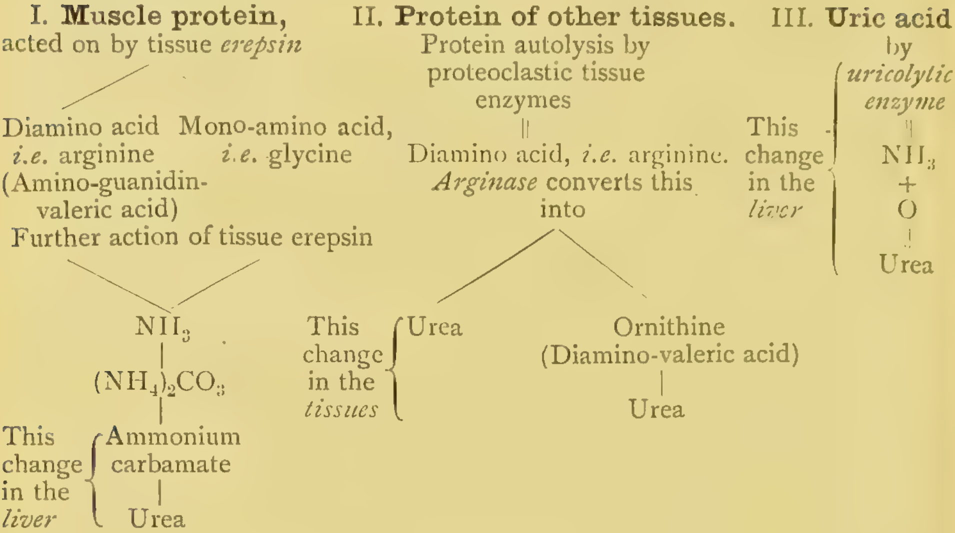
Does Urea rise entirely in the liver?—It seems clear that all the urea which is excreted does not come from the liver. Thus if the liver is excluded by means of an "Eck's fistula," it is often found that there is no alteration in the ratio of the amount of urea and ammonia excreted. A similar phenomenon is very frequently seen in cases of most profound disturbance of liver function: the absolute and relative amounts of urea and ammonia remaining unaltered.

Is Urea of Endogenous or Exogenous Origin?—The amount of urea in the urine varies in a remarkable manner with the amount of protein in the food. Increase of protein diet leads to great increase in the amount of urea excreted, whilst starvation causes an absolute diminution of the amount of urea in the urine. These results have led Folin to place urea amongst the products of exogenous metabolism. At the same time, however, a small amount must be regarded as of endogenous origin; for it is found that on increased work, which necessarily means increase of muscle waste, *i.e.* of the endogenous katabolic processes, there is an increase in the amount of urea excreted the day *after* the performance of the work.

The following table represents the formation of urea in the body.

Exogenous Urea is formed in the liver from ammonia and from simple amino-acids which have been absorbed from the intestine. The proper variety and amount of amino-acids are reconstructed into tissue proteins, according to the needs of the tissues, the useless and excess of amino-acids are converted into the comparatively inert substance urea, to be excreted by the kidneys.

Endogenous Urea is derived from the tissue proteins thus.—


I. Muscle protein,
acted on by tissue erepsin
Diamino acid i.e. arginine (Amino-guanidin-valeric acid)
Mono-amino acid, i.e. glycine
Further action of tissue erepsin
NH_3
$(NH_4)_2CO_3$
This change in the liver
Ammonium carbamate
Urea
II. Protein of other tissues.
Protein autolysis by proteoclastic tissue enzymes
Diamino acid, i.e. arginine.
Arginase converts this into
This change in the tissues
Urea
Ornithine (Diamino-valeric acid)
Urea
III. Uric acid
by uricolytic enzyme
This change in the liver
NH_3
+
O
Urea

Ammonia.

A small portion of the total nitrogen of the urine makes its appearance as ammonium salts. Under ordinary conditions of health and diet the amount excreted averages 0·5 to 1·5 grm. daily. The proportion of ammonia N to urea N is usually about 1 : 20.

The amount of ammonia in the urine varies inversely with the amount of urea,—that is to say, an increase in the amount of one of them is associated with a diminution in that of the other. The ammonia excreted represents so much ammonia, which, owing to the conditions prevailing in the body, has been prevented from undergoing the further change to urea. These conditions depend upon the supply of bases furnished to the body, and the extent of the latter's production of acid.

Under the normal conditions of metabolism, acids are constantly produced which, if allowed to accumulate, would give rise to the conditions known as acidosis. The necessary antidote is furnished by the bases in the food ; and it is quite possible that some of the excess of protein taken as food is useful in liberating NH_3 for the neutralisation of acids produced in the body. If, however, this alkali is not sufficient, a physiological remedy is furnished in the shape of the ammonia of the protein of the tissues. This is well shown in the case of feeding with animal and vegetable foods. With a diet poor in bases, such as animal material, it is found that the ammonia excretion is increased, whilst administration of the bases—rich vegetable material—causes a diminution in the ammonia excretion. It also follows from what has been said that administration of fixed alkali will lead to diminution of the urinary ammonia, as most of the ammonia is now converted into urea, while dosing with acids will have an opposite effect.

A fact standing in close relationship to the statements above is that increased muscular work leads to an increased elimination of ammonia salts in the urine. This is due to the great increase of acids produced as the result of the muscular work.

It is interesting also to notice the effects of feeding with different ammonium salts. Ammonium chloride, sulphate, and other inorganic acid compounds are excreted in the urine unchanged. Ammonium carbonate is excreted as urea. Ammonium tartrate, formate, citrate are excreted also as urea. In these cases the salt is probably first changed into the carbonate and then into urea, for it is well known that the alkaline salts of the above acids are excreted as carbonates.

In certain diseases of the liver, such as advanced cases of chronic alcoholic cirrhosis, and more particularly if the diseases are associated with granular kidneys, the precursors of urea, especially ammonia, accumulate in the blood, and death follows from auto-intoxication and convulsions (ammonæmia).

In diabetes mellitus there is an excessive formation of acids in the body; the result is that acidæmia occurs and death may take place from coma (diabetic coma). The physiological remedy and preventive for this is an increased production of ammonia by the tissues; the excess of the ammonia, however, passes over into the urine.

In normal circumstances, the production of ammonia by the tissues is kept at a minimum, the ammonia being finally converted, by the liver and in the tissues, into the less toxic substance urea. It should be noted that the arterial blood contains about two mgrms. per cent. of ammonia, whereas the portal blood contains six to eight mgrms. per cent., which suggests that the liver is the chief region where ammonia is being constantly changed into urea.

Creatinine and Creatine.

Creatinine has the composition $C_4H_7N_3O$. It is formed by the liver cells from substances of unknown composition, which are carried to the liver by the blood stream (possibly from the creatine of the food which has been absorbed by the small intestine). According to Mellanby, the creatinine formed in the liver is carried by the blood stream to the muscles, where it is stored as creatine (methyl-guanidine-acetic acid).

$$\underset{\text{(Creatinine)}}{C_4H_7N_3O} + H_2O = \underset{\text{(Creatine)}}{C_4H_9N_3O_2}$$

Creatine is present in the muscles to the extent of 0·4 per cent. It seems that creatine is necessary for the maintenance of the irritability of the motor end organs in striated muscle. When the limit of saturation of the muscles for creatine is reached, the creatinine, which is supplied to the muscles, is no, longer converted into creatine, but is eliminated in the urine as such. The amount of creatinine excreted in the urine in twenty-four hours is about 15 grms., and this amount remains remarkably constant; diet and exercise appear to have no effect upon it.

Creatine does not occur normally in urine. It is present in the urine, however, in certain abnormal conditions, such as starvation, specific fevers, after pregnancy, during involution of the uterus, and cases associated with muscular atrophy.

What eventually happens to the muscular creatine is unknown, but it is quite possible that some of it, at any rate, is split into urea and sarcosine.

$$\underset{\substack{\text{(Creatine}\\ \text{or}\\ \text{Methyl-}\\ \text{guanidine-acetic acid)}}}{C_4H_9N_3O_2} + H_2O = \underset{\text{(Urea)}}{CO(NH_2)_2} + \underset{\substack{\text{(Sarcosine, or}\\ \text{Methyl-glycine, or}\\ \text{Methyl-amino-}\\ \text{acetic acid)}}}{C_3H_7NO_2}$$

This change can be brought about by boiling creatine with baryta water.

Hippuric Acid.

Hippuric acid occurs in small quantities in the urine of man and carnivorous animals. In that of herbivorous animals, however, it may reach a large amount. The usual daily excretion of man averages 0·7 grm.

That so small amount is excreted may be readily understood when its mode of origin is considered. Hippuric acid on hydrolysis yields two bodies, glycocoll, or glycine, and benzoic acid.

$$\underset{\text{(Hippuric acid)}}{C_6H_5.CO.NH.CH_2.COOH} + H_2O = \underset{\text{(Benzoic acid)}}{C_6H_5COOH} + \underset{\text{(Glycocoll)}}{CH_2NH_2.COOH}$$

One of these, benzoic acid, is a body derived almost entirely from the food ; the other glycine (glycocoll or amino-acetic acid), may be derived by the process of either exogenous or endogenous protein metabolism. It is easy to understand, then, that the occurrence of hippuric acid in the urine stands in the most intimate relation to the presence and quantity of benzoic acid in the food. That is to say, a man fed upon a "benzoic acid free" diet will excrete no hippuric acid ; if given a diet containing large amounts of benzoic acid (*i.e.* if fed largely upon fruits) he will eliminate a much larger quantity of this acid.

In the case of man and the carnivora, the union of the two constituents of hippuric acid is effected in the kidney. This was first demonstrated by Bunge and Schmiedeberg, who showed that, if benzoic acid was circulated through the kidney of a dog, hippuric acid was formed. The amount formed was much increased if, at the same time, glycine was added to the circulating fluid. It has been since shown that the synthesis is due to the activity of an intracellular enzyme contained in the kidney cells.

In the herbivora hippuric acid appears to be also formed in other tissues.

Sulphur-containing Bodies.

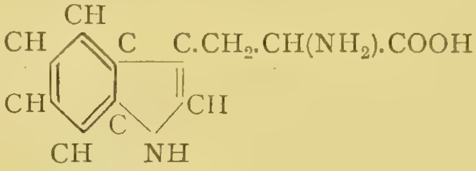
Sulphur is a constituent of most proteins (except protamines, histones, and infra-proteins), and the question of its formation and excretion occupies just as important a position as does the consideration of the nitrogenous metabolic products. In the first place, the sulphur is excreted chiefly in the urine, and to a very much less extent in the fæces. In the urine the sulphur-containing bodies may be divided into three groups :—

1. The inorganic or simple sulphates.
2. The ethereal or conjugated sulphates.
3. The organic or neutral sulphur.

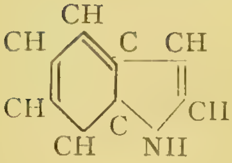
1. **The Inorganic Sulphates.**—These are regarded as being chiefly derived from the exogenous metabolism of proteins in the food.

2. **The Ethereal Sulphates.**—These occupy a peculiar position, and are of importance from a chemical standpoint. They are to some extent a measure of endogenous metabolism, but to a much greater extent they are derived from putrefactive processes which occur in the intestine. These bodies are compounds of sulphuric acid with potassium and indoxyl, skatoxyl, phenol, and cresol.

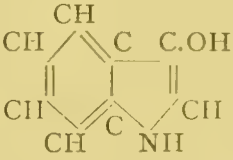
Skatoxyl and indoxyl arise by bacterial putrefaction from tryptophane (indole-amino-propionic acid). From this body indole and skatole are split off, and subsequently oxidised to indoxyl and skatoxyl. The relation between these different bodies is thus indicated chemically.



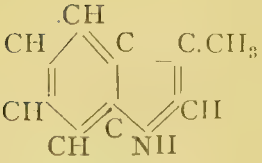
(Tryptophane)



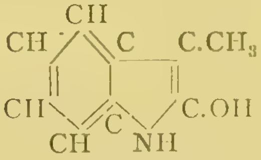
(Indole)



(Indoxyl)

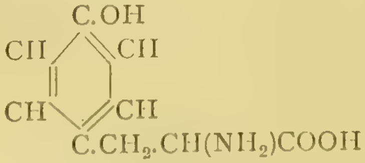


(Skatole)

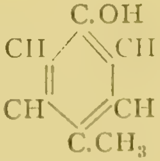


(Skatoxyl)

Cresol similarly is a derivative of tyrosine (oxyphenyl-alanine).

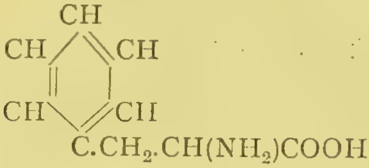


(Tyrosine)

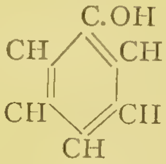


(Cresol)

Phenol is a further product of tyrosine, and might also be derived by oxidation of the phenyl ring of phenylalanine.

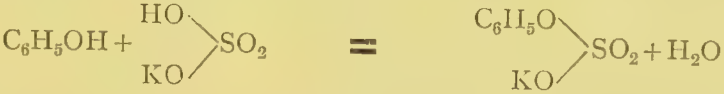


(Phenyl-alanine).

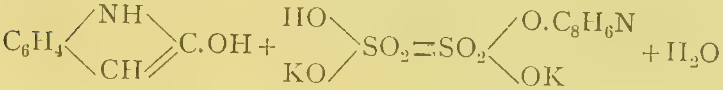


(Phenol)

The bodies thus produced in the intestine by bacterial action, especially in the large intestine, are phenol, cresol, indole, and skatole. Part of these are excreted in the fæces, the remainder are absorbed, and, after oxidation (indole to indoxyl and skatole to skatoxyl), are combined with sulphuric acid and excreted in the urine. The combination of phenol and indoxyl with sulphuric acid is represented in the following equations :—



$$C_6H_5OH + \begin{matrix}HO\\KO\end{matrix}\!>SO_2 = \begin{matrix}C_6H_5O\\KO\end{matrix}\!>SO_2 + H_2O$$



$$C_6H_4<\begin{matrix}NH\\CH\end{matrix}>C.OH + \begin{matrix}HO\\KO\end{matrix}\!>SO_2 = SO_2<\begin{matrix}O.C_8H_6N\\OK\end{matrix} + H_2O$$

(Indoxyl) (Indoxyl sulphate of K)

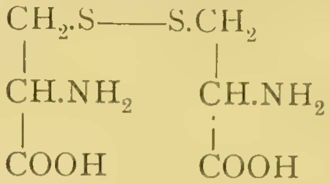
3. **Neutral Sulphur.**—This, according to Folin, is derived ntirely from protein katabolism. It consists chiefly of nethyl mercaptan, CH_3SH ; ethyl sulphide, $(C_2H_5)_2S$; otassium thio-cyanate, KCNS ; and a number of other less nown bodies.

The products of metabolism so far mentioned are the ormal end products of protein metabolism ; occasionally, owever, other substances are found in the urine which nust be looked upon as evidences of deranged metabolism.

The presence of amino-acids in the urine has been referred o in connection with atrophic cirrhosis of the liver. The resence of cystine and alcapton in the urine will now be eferred to.

Cystinuria.

This is an abnormal condition. Cystine is a sulphurontaining cleavage product of endogenous protein, and this abnormal metabolism runs in families; in other words, it is an hereditary condition. Cystine has the following formula :—

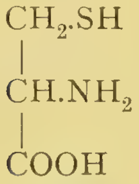


$$\begin{array}{ll} CH_2.S\text{———}S.CH_2 \\ | \qquad\qquad\quad\ | \\ CH.NH_2 \quad CH.NH_2 \\ | \qquad\qquad\quad\ | \\ COOH \qquad COOH \end{array}$$

(Cystine or diamino-dithio-dilactic acid)

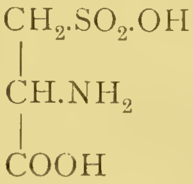
Keratin is rich in cystine, which can be readily prepared from hair.

On reduction cystine yields cysteine (amino-thio-propionic acid). Cysteine, on oxidation, yields cysteinic acid, and this splits into taurine and carbon-dioxide. There is a great deal of evidence that the taurine of the bile is the source of the cystine of the urine. The following formulæ indicate the relationship of cysteine, cysteinic acid, and taurine :—



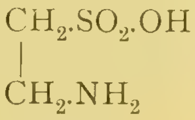
$$\begin{array}{l} CH_2.SH \\ | \\ CH.NH_2 \\ | \\ COOH \end{array}$$

(Cysteine)



$$\begin{array}{l} CH_2.SO_2.OH \\ | \\ CH.NH_2 \\ | \\ COOH \end{array}$$

(Cysteic acid)

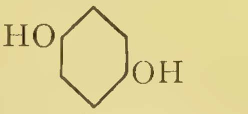


$$\begin{array}{l} CH_2.SO_2.OH \\ | \\ CH_2.NH_2 \end{array}$$

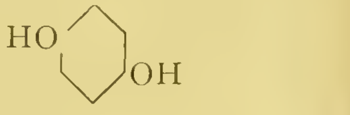
(Taurine)

Alcaptonuria.

In this condition two organic acids of an aromatic nature are found in the urine, homogentisinic acid and uroleucic acid.



(Homogentisinic acid)

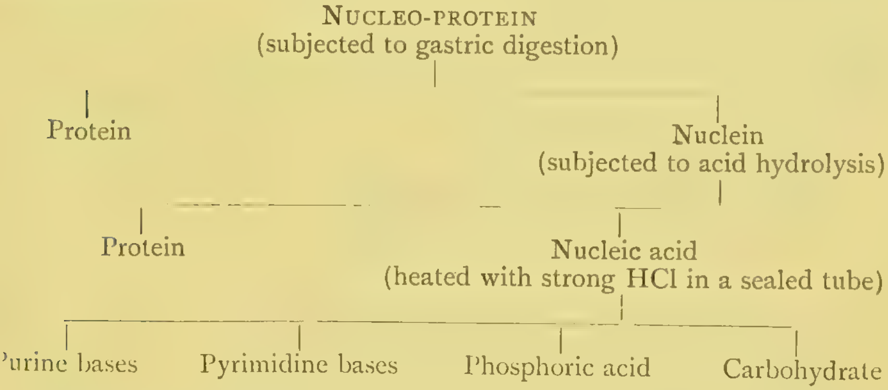


(Uroleucic acid)

These acids are derived from proteins which contain aromatic radicals such as phenyl-alanine or phenyl-amino-propionic acid ($C_6H_5.C_2H_3.NH_2.COOH$) and tyrosine or oxyphenyl-amino-propionic acid [$(C_6H_4.OH)C_2H_3.NH_2.COOH$]. Alcaptonuria is an hereditary condition, and usually indicates a congenital and lifelong abnormal protein katabolism. With alcaptonuria, "ochronosis—blackening of the cartilages and ligaments, and sometimes of the conjunctivæ—may occur. Usually there is a chronic arthritis also, which may lead to a curious 'goose-gait'" (Langdon Brown).

NUCLEO-PROTEIN METABOLISM.

The chemistry of "nucleo-proteins" indicates that they consist of nucleic acid combined with protein. All the protein does not appear to stand in the same relationship to the nucleic acid component—one portion seems to be more closely combined than another, for, on peptic digestion, the nucleo-proteins do not yield nucleic acid and protein directly, but a white insoluble nuclein and protein. Nuclein, on further hydrolysis, such as is effected by mineral acids, yields more protein and nucleic acid. Nucleic acid, hydrolysed with strong hydrochloric acid in a sealed tube, and heated to a considerable temperature, yields purine bases, pyrimidine bases, phosphoric acid, and a carbohydrate (usually a pentose, namely, xylose). These reactions may be expressed diagrammatically thus:—


NUCLEO-PROTEIN
(subjected to gastric digestion)
Protein
Nuclein
(subjected to acid hydrolysis)
Protein
Nucleic acid
(heated with strong HCl in a sealed tube)
Purine bases
Pyrimidine bases
Phosphoric acid
Carbohydrate

The products of hydrolysis will be further considered.

The Purine Bases.—These are a group of bodies so called because of their close relationship to purine, the mother ubstance of the group. The purines are sometimes called he alloxuric bases. The members of physiological importance are—

1. Oxidation derivatives—
    Hypoxanthine.
    Xanthine.
    Uric acid.
2. Amino derivatives—
    Adenine.
    Guanine.

The close chemical relationship of these different bodies is indicated in these formulæ :—

$C_5H_4N_4$	Purine.
$C_5H_4N_4O$	Hypoxanthine (monoxypurine).
$C_5H_4N_4O_2$	Xanthine (Dioxypurine).
$C_5H_4N_4O_3$	Uric acid (Trioxypurine).
$C_5H_3N_4.NH_2$	Adenine (amino-purine).
$C_5H_3N_4O.NH_2$	Guanine (amino-oxypurine).

It is important to notice here the close relationship existing between adenine ($C_5H_3N_4.NH_2$) and hypoxanthine ($C_5H_4N_4O$) ; and between guanine ($C_5H_3N_4O.NH_2$) and xanthine ($C_5H_4N_4O_2$); how, by the replacement of NH in each case by O, hypoxanthine and xanthine are respectively formed.

The nucleic acid, isolated from the cells of the pancreas, contains guanine only, whereas the nucleo-protein derived from the cells of the thymus contains the purine base, adenine only.

The Pyrimidine Bases are three in number, and are derived from the mother substance pyrimidine ($C_4H_4N_2$). They are

Uracil, or dioxypyrimidine . . . . $= C_4H_4N_2O_2$.
Thymine, or methyl uracil . . . $= C_4H_3.CH_3.N_2O_2$.
Cytosine, or amino-oxypyrimidine . $= C_4H_4N_2.O.NH_2$.

A. Anabolism.

The anabolism of the nucleo-proteins is a subject concerning which very few facts are known. Obviously the protein component will be formed in the same fashion as the protein bodies generally (already described under "Anabolism in Protein Metabolism"). On the other hand, the nucleic acid constituent presents greater difficulties ; it appears to be produced only from the nucleic acid ingested, or from purine bases, and in the mammal, at any rate, appears not to be formed from simpler materials.

B. Katabolism.

The katabolism of the nucleo-proteins is a subject presenting unusual features of interest. Recent investigations seem to indicate that it must be due to the action of intracellular enzymes (endo-enzymes), and by studying the action of these different enzymes, it has been possible to get a clear, connected idea of the progress of disintegration in the nucleo-protein molecule.

The first katabolic change in the nucleo-protein seems to be the splitting up of the molecule into protein and nuclein. The former undergoes subsequent katabolic changes, resulting in the formation of ammonia, urea, etc., in precisely the same way as the ordinary proteins. The nuclein undergoes a further decomposition with the production of adenine and guanine. This change is due to the activity of an enzyme (nuclease) which has been shown to exist in certain organs, such as the liver, spleen, and kidney. Adenine and guanine may be in part excreted in this form; the greater part, however, undergoes further changes with the formation of hypoxanthine and xanthine, and the release of ammonia in each case. This action is of a hydrolytic character, and is due to the activity of a separate enzyme in each case, adenase and guanase respectively. A small part of the xanthine and hypoxanthine so produced may also find its way into the urine, but the major share undergoes oxidation, due to oxidising enzymes (xanthine oxidases), resulting in the production of uric acid. But again the changes do not stop here: all the uric acid formed is not excreted as such, but half of the total quantity is destroyed by the agency of a liver endo-enzyme (the uricolytic or uricoclastic enzyme) with the formation of urea.

The following table shows these changes just described:—

NUCLEIN
is converted by *Nuclease* into

Amino-purine
or
Adenine;
this is converted by *adenase* into

Monoxypurine or hypoxanthine;
this is converted by *oxidase* into

Dioxypurine or xanthine;

Amino-oxypurine
or
Guanine;
this is converted by *guanase* into

Dioxypurine of xanthine;

this is converted by *xanthine-oxidase* into

Trioxypurine or uric acid;
much of this is converted by the uricoclastic enzyme of the liver into

Urea.

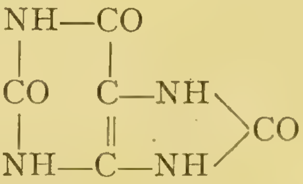
The changes indicated above take place both in the nucleo-protein ingested and nucleo-protein of the tissues. The former may be distinguished as exogenous katabolism, the latter as endogenous katabolism.

Consequently, from what has been mentioned, it is obvious that the end products of nucleo-protein metabolism, whether endogenous or exogenous, are adenine, guanine, hypoxanthine, xanthine, and uric acid. Of these, uric acid will now be considered, because it is by far the most important of the purines excreted (in the urine, the proportion of uric acid present to other purines is as 4 to 1), and also because the detailed consideration of its formation will throw light upon the formation of the others.

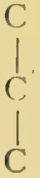
URIC ACID.

Occurrence of Uric Acid.—Uric acid is the most important end product of nucleo-protein metabolism. Some of the uric acid produced in the body is eliminated in the urine, and, after urea and creatinine, comes quantitatively as the third most important form of nitrogen excretion. In mammals it occurs in the urine to the extent of 0·05 per cent.; the total excretion for the day being on the average 0·75 grm. In birds and reptiles it is the chief nitrogenous excretion. In normal circumstances it is absent from the sweat.

Chemistry of Uric Acid.—Uric acid, considered chemically, is closely related to urea, for it consists of two molecules of urea united to a central carbon chain containing three carbon atoms; that is to say, it is a diureide. This is readily understood from its formula—

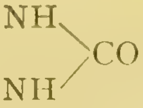


It will be noticed that in the centre is the carbon chain

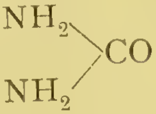


$$\begin{array}{c} C \\ | \\ C \\ | \\ C \end{array}$$

united on either side to a urea radical



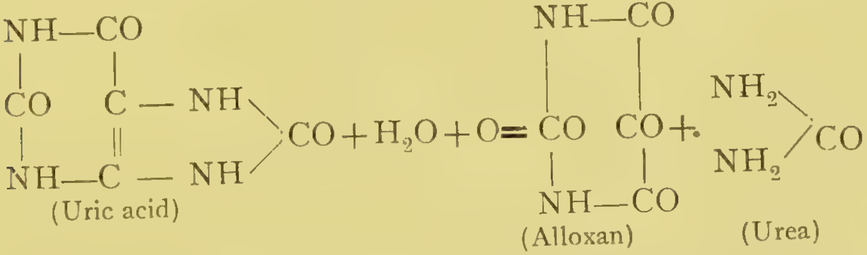
Urea is the diamide of carbonic acid, being



$$\mathrm{(NH_2)_2CO}$$

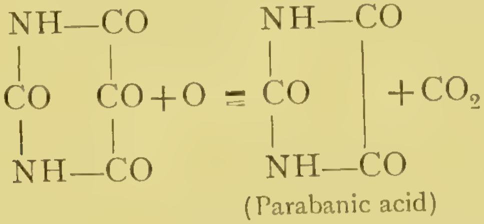
If the decomposition of uric acid is effected by appropriate reagents it is possible to split off one urea molecule, leaving a monoureide, and by still further treatment to destroy this monoureide in such fashion that another urea molecule is split off. That is to say, both urea molecules can be prepared from uric acid by appropriate methods. These methods are as follows:—

1. Uric acid on treatment with nitric acid breaks up into alloxan and urea.



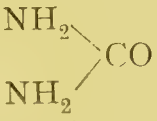
(Uric acid) (Alloxan) (Urea)

2. Alloxan, warmed with nitric acid, yields parabanic acid—

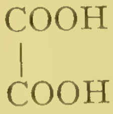


(Parabanic acid)

It is to be noticed that parabanic acid is the monoureide of oxalic acid—

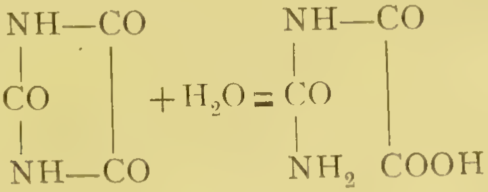


(Urea)



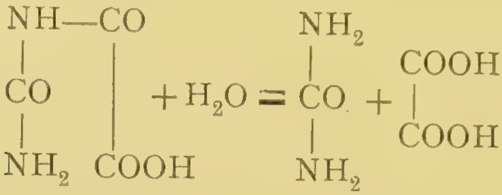
(Oxalic acid)

3. Parabanic acid, heated with alkali, yields oxaluric acid—



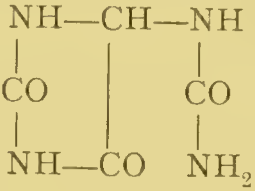
(Oxaluric acid)

4. Oxaluric acid, boiled with water, yields the second urea molecule, and oxalic acid—



$$\begin{array}{ll}\mathrm{NH}\text{—}\mathrm{CO} & \\ | & | \\ \mathrm{CO} & | \\ | & | \\ \mathrm{NH_2} & \mathrm{COOH}\end{array} + \mathrm{H_2O} = \begin{array}{c}\mathrm{NH_2}\\ | \\ \mathrm{CO}\\ | \\ \mathrm{NH_2}\end{array} + \begin{array}{c}\mathrm{COOH}\\ | \\ \mathrm{COOH}\end{array}$$

Another decomposition of considerable interest is that, on being heated with potassium permanganate, uric acid yields allantoin—

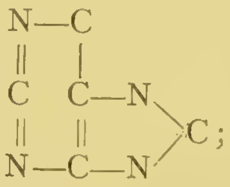


$$\begin{array}{lll}\mathrm{NH} & \text{—CH—} & \mathrm{NH} \\ | & | & | \\ \mathrm{CO} & | & \mathrm{CO} \\ | & | & | \\ \mathrm{NH} & \text{—CO} & \mathrm{NH_2}\end{array}$$

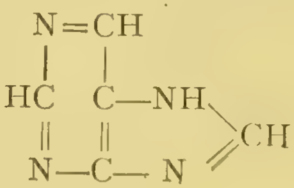
This stands in relation with the observation that dogs yield allantoin in the urine on the administration of uric acid.

Uric acid also yields glycine on being heated in a sealed tube with water. Horbaczewski has succeeded in synthesising uric acid by heating urea and glycine together in a sealed tube.

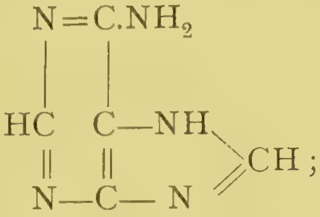
Formation of Uric Acid.—This has been already dealt with in the section upon the "Katabolism of the Nucleo-Proteins." There it was shown that the source of uric acid lies in the purine bases, whether these are of the food or of the tissues, and that these bodies were set free by the action of an intracellular enzyme (nuclease) of wide distribution. The purine nucleus, from which the different bodies are derived, is represented structurally, thus—



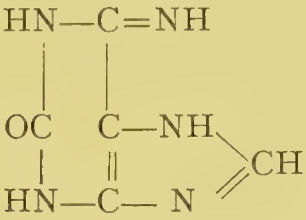
the hydrogen compound of this being purine itself—



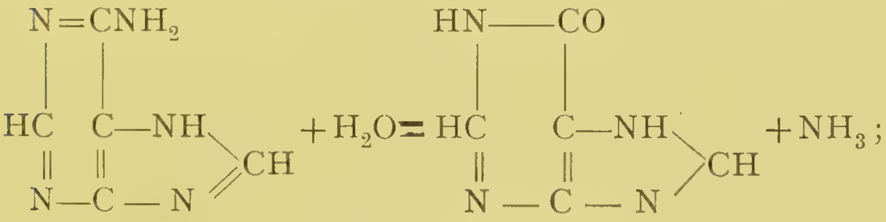
On substitution of one H of this compound by NH_2, adenine is produced—



or, on oxidation and NH_2 substitution, guanine is produced—

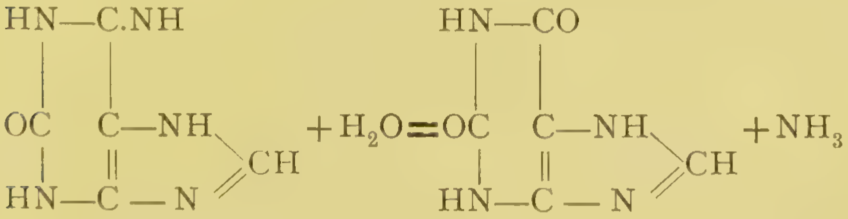


These bodies, adenine and guanine, are the purine bases which arise from nucleo-protein by the activity of the intracellular enzyme *nuclease*. The adenine and guanine are acted upon by *adenase* and *guanase* respectively, which split off the NH_2 groups as NH_3 and leave the residue oxidised. Thus adenine yields hypoxanthine—



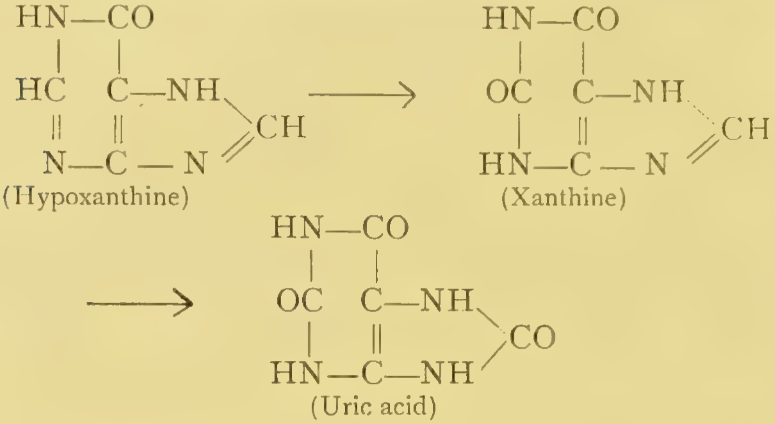
(Hypoxanthine)

whilst guanine similarly yields xanthine—



(Xanthine)

The hypoxanthine and the xanthine thus produced then undergo oxidation into uric acid—



These oxidative changes are due to the activity of enzymes, chiefly found in the liver cells and known as xanthine oxidases. Thus, putting the series of changes by which uric acid is formed from the nucleo-protein of the diet (exogenous metabolism), or the nucleo-protein of the tissues (endogenous metabolism), into schematic form :—

1. Nucleo-protein is split into protein and nuclein (in the case of ingested material, gastric juice will effect this change).

2. Nuclein is split up with the production of adenine and guanine by the endo-enzyme nuclease.

3. Adenine and guanine are deamidised with the production of hypoxanthine and xanthine respectively, by the activity of adenase and guanase.

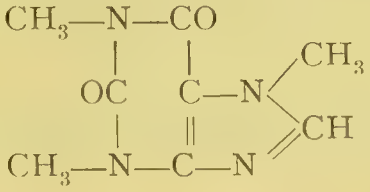
4. Uric acid is produced by the oxidation of hypoxanthine and xanthine; due to the activity of xanthine oxidases.

It is then fairly well established that uric acid arises from nucleo-protein metabolism, whether endogenous or exogenous. Also it is obvious that uric acid will arise from any hypoxanthine or xanthine administered experimentally; about half of the administered purines reappear in the urine as uric acid. But this is not all, when a person is put on a diet of purine-free material (milk, eggs, bread) it is found that the excretion of purines falls to about half its former level, and then remains constant. This indicates the extent of tissue nucleo-protein metabolism; and it is found on exercise that purine excretion is immediately increased, the purine bases first and then the uric acid. Further, on perfusing a dog's hind-limb with defibrinated blood and Ringer's solution, it is found that there is an increase of uric acid in the blood from the part, and also of uric acid and hypoxanthine in the muscles, indicating that muscles are also possibly a source of uric acid.

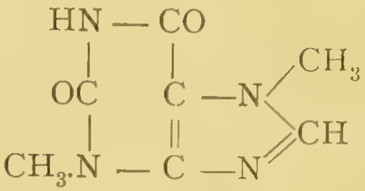
Hence it may be concluded that uric acid arises from (1) nucleo-protein metabolism, and (2) the muscles; and further, from the feeding experiments already mentioned, under ordinary conditions, half of the uric acid formed in the body is destroyed, and of that which appears in the urine half is derived from endogenous and exogenous metabolism.

What becomes of the Uric Acid destroyed?—It has been already pointed out that part of the uric acid produced in the body is destroyed. In the case of the carnivorous animals it is destroyed in the liver; in herbivorous animals it is destroyed in the kidney. The destruction is due to the action of an intracellular enzyme (the uricolytic or uricoclastic enzyme), and appears to ultimately result in the production of urea. Whether the intermediate bodies produced are allantoin or glycine, in the case of the carnivora, is not exactly known (in the case of herbivora, glycine is certainly an intermediate decomposition product (Wiener)), but it is certain that the body finally formed is urea. In different animals the amount so destroyed also varies,—thus, in man, half of the total uric acid produced is excreted in the urine; in the case of cats and dogs, only one-twentieth.

The Influence of Diet on the Excretion of Purines.—It has been pointed out that feeding with xanthine or hypoxanthine results in an increased amount of uric acid in the urine; similarly adenine and guanine cause an increase in the other purine constituents of the urine (adenine, guanine, hypoxanthine, and xanthine); consequently, on administering beef-tea or meat extract to an animal there is an increased amount both of uric acid and the other purines of the urine. A point arises here in connection with the administration of tea, coffee, and cocoa, as to whether tea and cocoa, which contain bodies closely related to the purine bases, have any effect upon the uric acid and purine excretion. Caffeine, the active principle of tea, is trimethylxanthine, a body with the formula



Whilst theobromine, the active constituent of cocoa, is dimethylxanthine, represented by



It is found that administration of these bodies does not lead to an increased amount of uric acid, although it causes an increase in the quantity of purine bases excreted. The source of urinary purines may be classified as follows (Langdon Brown):—

1. Exogenous Purines from the food—
    - (*a*) Methyl-purines in tea, coffee, cocoa. Theobromine, or dimethylxanthine ($C_5H_2.(CH_3)_2N_4O_2$). Theine and caffeine, or trimethylxanthine ($C_5H.(CH_3)_3N_4O_2$).
    - (*b*) Free purines, such as hypoxanthine ($C_5H_4N_4O$) and xanthine ($C_5H_4N_4O_2$) in meat extracts.
    - (*c*) Bound purines in the tissue cells (nucleo-pretein).
2. Endogenous Purines from the katabolism of the nucleo-proteins of the cells, including the white blood corpuscles, and especially muscle fibres of the body. It has been already stated that on a "purine-free" diet the urine contains purine bodies.

It must be remembered, however, in the case of birds and reptiles which pass a solid urine consisting chiefly of urates, that uric acid is synthesised in the liver from substances which do not contain a purine ring at all,—namely, ammonia and lactic acid. There is no reason to believe that much uric acid is produced in this way in man; still, it is quite possible that a small amount may be produced in the liver by a similar synthesis.

The uric acid, which is excreted in the urine, occurs there as the acid sodium urate ($C_5H_3NaN_4O_3$) and the normal sodium urate ($C_5H_2Na_2N_4O_3$). Under abnormal conditions (gout), uric acid may be excreted by the kidney as such, a circumstance due to the fact that the liver is not doing its work properly, *i.e.* hepatic insufficiency, and consequently the purines are not well metabolised.

PHOSPHORUS-CONTAINING BODIES.

The chief compounds in the body which contain phosphorus are nucleo-protein, nuclein, nucleic acid, and the phosphatides—lecithin, kephalin and sphingomyelin, which occur for the most part in nerve tissue. The phosphorus necessary for the anabolism of these bodies is derived from that contained in the food, such as nucleo-protein of meat and fish, and phospho-protein of milk and eggs, and the phosphates contained in milk, etc. The phosphates, which are excreted in the urine, amount to about 2·5 grms. per diem, and are derived from the food (exogenous phosphates), and from the katabolic changes which take place in the phosphorus-containing bodies in the tissues, such as nucleo-protein, nuclein, lecithin, etc. (endogenous phosphates). In certain wasting diseases, in which there is increased katabolism of nucleo-proteins, etc., there is an increased formation of phosphates in the body, and consequently an increased elimination of phosphates in the urine. On the other hand, in pregnancy and in convalescence after illness, phosphates diminish in the urine, as they are required for the anabolism of the phosphorus-containing compounds of the body.

CHAPTER XXVIII.

CARBOHYDRATE METABOLISM.

A. Anabolism.

Carbohydrate in Food and Changes in Digestion.—The chief supply of sugars to the body is provided in the form of the disaccharides (cane sugar and lactose), and of the polysaccharides (starches). During the processes of digestion these carbohydrates are resolved into their simple monosaccharide components—dextrose, lævulose, and galactose.

Meaning of Cleavage.—The splitting up of the more complex carbohydrates is of great significance. First, it takes place in order to form readily diffusible and assimilable bodies; and, in the next place, it furnishes a pabulum of constant composition to the body, so that from the most diverse carbohydrates foreign to the organism the body is able to form sugars with the constitution of which it is acquainted, sugars which it can utilise in the production of its own peculiar carbohydrates.

The significance of the cleavage is made apparent by the following experiment. When a foreign sugar is introduced into the blood stream of an animal by a method which avoids the disintegrative action of the digestive enzymes, it is at once excreted, unchanged, into the urine. Thus, if cane sugar is injected into the blood stream of an animal, it is excreted in the urine unchanged. On the other hand, if maltose, a similar disaccharide, is injected into the blood of an animal it is utilised in the body. The reason is not far to seek. Inversive enzymes, converting cane sugar into its derivative monosaccharides, are not to be found in any tissue of the body except the intestinal mucosa. The enzyme *maltase*, however, is of extremely wide distribution, and is found in many tissues and organs of the body, the greatest amount being in the liver. It is not surprising, then, that maltose is utilised, for it can be readily resolved into its constituent molecules of dextrose.

Absorption of Sugars.—The sugars absorbed are the monosaccharides—dextrose, lævulose, and galactose. They are transferred, by the columnar epithelial cells covering the villi of the small intestine, into the blood stream of the portal vein radicals. None of the carbohydrate food material is absorbed into the lacteals. The surface offered for absorption is large; the carbohydrates are readily resolved into their constituent monosaccharides. Moreover, monosaccharides are very soluble and readily dialyse; hence, of all the food stuffs, sugars are the most readily assimilable.

Sugar in the Portal Blood.—From the intestinal capillaries the blood, containing the absorbed sugar, passes into the portal vein and so to the liver. The determination of the exact quantity and nature of sugar present in the blood is a matter of great technical difficulty; but the results of the more recent investigations show that the percentage of sugar in the portal blood varies, although within narrow limits (0·05, 0·2, and 0·4 per cent.). The lowest figure is reached only in advanced starvation, and in this condition the sugar percentage remains constant. The higher results are only reached when the sugar content is estimated from portal blood obtained from an animal during the digestion of a meal rich in carbohydrate material.

Sugar Content of General Systemic Blood.—When the percentage of sugar is estimated from the blood obtained from the general circulation of an animal, the remarkable fact at once becomes apparent that the sugar content of this blood is fairly constant, varying only within narrow limits. The amount present varies between 0·05 and 0·15 per cent. This amount is constant even in advanced starvation (when the percentage of sugar in the portal blood falls also to the same figure), or if estimated during the course of a meal moderately rich in carbohydrates. It never transgresses beyond these narrow limits. It will be pointed out later that there are certain abnormal conditions in which the percentage of sugar in the blood rises beyond the limits already mentioned. Sugar occurs in the blood in a free, not in a combined, state. Formerly it was thought that it existed in the blood stream in combination with other substances, such, for example, as the proteins of the blood; but recent researches, carried out by Asher and Rosenfeld, have demonstrated the incorrectness of this assumption.

Sugar Storage.—From a consideration of the facts mentioned in the preceding paragraphs—

(1) That the sugar percentage of the systemic blood is constant;
(2) That sugar percentage of portal blood varies, being high during digestion of carbohydrates, but never falling below that of the systemic blood;
(3) From the figures already quoted for the sugar content of the blood, that 10 grms. only of sugar can be thus accounted for as existing therein, the following conclusions must be drawn:—

1. That there must be some place or places for the storage of sugar in the animal body. This storage need not be of necessity, though it may be, in the form of sugar. It might exist, for example, as fat. This conclusion is reached because it is not conceivable that the sugar is utilised immediately it is absorbed; and,

2. That there must be a place where the percentage of sugar in the systemic blood is regulated. This conclusion is especially patent if another point is considered, which is, if the percentage of sugar in the systemic circulation is raised, even in the slightest degree, above the fixed upper limit of about 0·2 per cent., sugar is immediately excreted in the urine. Hyperglycæmia (excess of sugar in the blood) is followed by glycosuria (elimination of sugar in the urine). The kidney acts as a filter, by which any excess of blood sugar is immediately removed.

Returning to the conclusions arrived at, there must be in the body somewhere an organ or organs whose function it is to store up sugar, and at the same time to regulate the amount of sugar present in the systemic circulation. The chief organ is the liver, and others, to a much less extent, are the skeletal and cardiac muscles. These will be discussed separately.

Glycogenic Function of the Liver.—It is natural to suppose, from the facts already mentioned concerning the sugar content of the systemic and portal blood respectively, that the liver must play an important part in the metabolism of carbohydrate materials. Experimental evidence supports this view.

Some fifty years ago Claude Bernard made the important discovery that the amount of sugar in the freshly excised liver was very small, but that after a while, on standing, much sugar was rapidly formed in it. Claude Bernard drew the deduction that this sugar must have arisen from some other substance than monosaccharide, and by subsequent research he succeeded in demonstrating this glycogenic substance. He showed, histologically, that the liver cells contain a substance stored up in their cytoplasm (not in their nuclei), and that this substance develops a port-wine colour when treated with a solution of iodine. He isolated this body by solution in dilute alkali and by precipitation with absolute alcohol, and proved its chemical nature to resemble that of starch; for it was a polysaccharide which on hydrolysis yielded dextrose. He gave to it the name **glycogen.**

Subsequent observers have shown that the amount of glycogen in the liver bears a certain definite relationship to the amount and nature of the carbohydrate food. Hence it is concluded that sugar absorbed in the intestine is carried to the liver by the portal blood stream, and that in the liver it is built up into the complex polysaccharide glycogen.

The post-mortem resolution of glycogen into sugar has been repeatedly demonstrated since Claude Bernard's original experiment, and it has been shown by numerous investigators to be due to the activity of a diastatic enzyme (amyloclastic) contained in the cells of the liver, *i.e.* to the activity of an intracellular enzyme. Maltose is formed as an intermediate product in the resolution.

GLYCOGEN,
acted upon by the diastatic enzyme
↓
Maltose ($C_{12}H_{22}O_{11}$)
↓
Dextrose ($C_6H_{12}O_6$)

Now, most enzymes are capable of acting in the reverse direction to that which they usually adopt, and this is particularly so in the case of *maltase* (the enzyme which hydrolyses maltose), in which this reversible action has been demonstrated by Croft Hill. Further, if yeast is used as a source of *maltase*, not only is maltose produced by the action of the yeast upon dextrose, but also certain bodies of a dextrin nature. These are produced by the reversed action of the amylolytic (amyloclastic) enzyme which it contains. It is natural, then, to assume that this sugar transformation into glycogen is due to the reversed action (caused and regulated by the conditions obtaining in the liver cells at the time), of the enzyme which produces sugar from glycogen. This, however, has never been completely demonstrated.

The amount of glycogen contained in the liver varies with the condition of the animal, and with the amount and nature of the food ingested previous to death. The maximum amount found has been as much as 10 per cent. of the total weight of the liver. In the case of an ordinary man, assuming his liver to weigh 1500 grms., the greatest quantity of glycogen contained in it would be 150 grms.

Source of Liver Glycogen.—It has been demonstrated by experiment that the amount of glycogen present in the liver depends, other conditions being equal, upon the amount and nature of the food material. Although, in the case of a well-nourished animal, the amount of glycogen present in the liver may reach the high figure of 10 per cent., the total weight of the organ, yet in an animal starved, even if the starvation has been continued for such a short time as ten days, the glycogen of the liver entirely disappears. From this it is clear that the liver glycogen bears an intimate relationship to the food material. In food, however, there are three distinct kinds of carbonaceous material—proteins, fats, and carbohydrates, and the question as to the origin of glycogen from these must be considered separately.

Glycogen from Carbohydrates.—That carbohydrates give rise to glycogen in the liver may be shown by the following experiment. Some dogs are starved, until experience teaches that the glycogen content of the liver is as low as possible (this usually takes about ten days). Half the dogs are then fed upon a rich carbohydrate diet, the starvation of the rest being continued. Subsequently all the dogs are killed, when it is found under these conditions that the livers of those recently fed contain large amounts of glycogen.

Grube has recently shown the same thing, but in a different way. He circulated defibrinated blood containing dextrose through the excised liver of a dog, and found an increase in the amount of glycogen present therein.

It seems that dextrose is the chief source of glycogen, though other monosaccharides, such as lævulose, are also converted into glycogen.

In this connection the question arises, whether these different sugars give rise to different glycogens, or whether the different sugars are all transformed into dextrose, and the dextrose into glycogen. It seems certain, from observations carried out on glycosuric animals, that lævulose, at least, is not converted into dextrose before becoming glycogen.

Glycogen from Proteins. — The method of determining whether a given material produces glycogen or not, as explained above in the feeding experiments, may be described as the "direct method of determination of the glycogen-producing value" of any given food material. Such a method of experiment, however, does not in all cases give a satisfactory result, and this is particularly the case with regard to the food material under consideration. For a long time observers, from the time of Claude Bernard, have repeatedly asserted that feeding proteins gives rise to an increase in the amount of glycogen in the liver, while other observers have just as positively and persistently denied this statement. Obviously, then, in order to obtain a satisfactory conclusion, other methods must be brought to bear upon the elucidation of this difficult problem. The "indirect method of determining glycogen value" is the fruit of these researches. The method depends upon the following considerations: that if any substance gives rise to the formation of sugar in the body, then that particular substance will be a glycogen former, for the liver will form glycogen from sugar, no matter where or how that sugar is produced. Now, it is possible to show definitely whether a given food material will or will not give rise to the formation of sugar in the animal body. In the animal it is possible, by means of certain operations, to so alter the metabolic machinery as to render the animal incapable of utilising sugar, so that sugar either introduced into the body or formed within the body, is excreted in the urine. If administration of any given food material should cause an increase in the amount of glucose excreted, then that material must be regarded as a source of sugar—and therefore a source of glycogen—in the animal body. The modes of production of this condition will be dealt with later on, and the influence of the different food materials upon the sugar excretion discussed. Here it suffices to state that such experiments have demonstrated that *protein must be regarded as a source of glycogen.*

Origin of Glycogen from Fat.—Fat is a mixture of the triglycerides of the saturated acids, palmitic and stearic acids, and the unsaturated oleic acid. With regard to the relationship of the fats to sugar production, experiments carried out on the lines mentioned above have failed to show that glycogen originates from the fatty acid component; proof is not lacking, however, that glycerin is an undoubted glycogenetic substance. This question also will be discussed presently at greater length.

What becomes of the Excess of Sugar in the Organism?—It is seen, then, that the liver is capable of building up, *i.e.* of synthesising glycogen from glucoses, from fats, and from proteins supplied to it; and further, that the maximum amount of glycogen stored up in the liver amounts to 150 grms. Similarly, the muscles also store up glycogen; the amount of glycogen so stored also amounts to about 150 grms. Consequently, between the liver and muscles the animal is able to store up 300 grms. of glycogen, so that a starving animal is able to reserve 300 grms. of carbohydrate material. With an animal in conditions of normal nourishment and health, the amount of sugar which can be so stored must be decidedly less, so that the excess of the 500 grms. of carbohydrate food material taken daily, and which does not undergo transformation into glycogen, has to be accounted for. It is manifestly absurd to believe that this sugar is destroyed on reaching the blood stream; such a destruction, at a moment when production of energy is not essential, would be waste. As a matter of fact, the excess of carbohydrate is stored up as fat; the experiments of Lawes and Gilbert, on the fattening of live stock, have amply demonstrated the truth of this common knowledge. It is also believed that a certain amount of sugar is, in addition, stored up *adsorbed* to protein.

B. Katabolism.

Destruction of Sugar in the Body.—Examination of the excreta does not reveal any sugar present in normal circumstances, urine, fæces, and sweat are alike free from it. Sugar must therefore be used up, or rather decomposed and eliminated from the organism in some other form than that of sugar. Examination of the respiratory products reveals that they contain carbon-dioxide and water; similarly, water is present in the urine and sweat, and carbon-dioxide also is eliminated in small quantities by the skin. Carbohydrates contain only carbon, hydrogen, and oxygen, so that it would seem to be a perfectly justifiable assumption that they are oxidised and excreted as carbon-dioxide and water,—an assumption the correctness of which is demonstrated by the consideration of the respiratory quotient after a meal of carbohydrate material. The respiratory quotient expresses the ratio of the volume of carbon-dioxide expired to that of oxygen inspired :—

$$R.Q. = \frac{CO_2 \text{ (vol.)}}{O_2 \text{ (vol.)}}$$

If the oxidation of sugar (monosaccharide) to carbon-dioxide and water is considered in a chemical formula, the following is obtained :—

$$C_6H_{12}O_6 + \underset{\text{(12 vols.)}}{6\ O_2} = \underset{\text{(12 vols.)}}{6\ CO_2} + 6\ H_2O$$

and from this is deduced (applying Avogadro's law that "equal volumes of gases, under the same pressure and temperature conditions, contain equal numbers of molecules") that

$$R.Q. = \frac{CO_2 \text{ (vols.)}}{O_2 \text{ (vols.)}} = \frac{12}{12} = 1$$

in other words, that the respiratory quotient should approach unity.

As a matter of experience it is found that, after a meal of carbohydrate alone, the respiratory quotient quickly approaches the value one, indicating that it is oxidised, and that with extreme rapidity, to carbon-dioxide (CO_2) and water (H_2O), the process being carried out according to the chemical equation given above.

Intermediate Bodies in the Destruction.—But while, as a matter of fact, such bodies are the final products of oxidation, the question as to what constitute the intermediate bodies formed during the attainment of this final condition still remains unsolved. Many hypotheses have been advanced, but only two need be mentioned here. The first view, and perhaps the most important, is that lactic acid is the first product formed, and that this is finally converted into carbon-dioxide and water. The second view is interesting, and has some experimental foundation for it, although it cannot be said that it should be unreservedly accepted. It assumes that the sugar is first broken up into carbon-dioxide and ethyl alcohol (C_2H_5OH), in a similar manner to the alcoholic fermentation of yeast—

$$C_6H_{12}O_6 = 2C_2H_5.OH + 2CO_2$$

The alcohol is then assumed to be further oxidised to carbon-dioxide and water. The experimental justification is furnished by Stoklasa. He claims to have demonstrated that a very large number of the different organs and tissues of the body (liver, muscles, lungs) possess enzymes, precipitated by alcohol-ether treatment, which are capable of effecting this alcoholic fermentation.

Use of Sugar in the Body.—The simplest way to study this question is by observing the fate of the glycogen of the body. It is found experimentally, that the glycogen content of the animal body is diminished, and if no food is given it ultimately disappears, under the following conditions :—

If food is completely withheld,
If work is performed,
If the animal is cooled ;

proving that glycogen serves for the production of muscle energy and heat energy in the body. Further, the glycogen disappears first and quickest in the muscles, and only later from the liver, showing that the muscles are the chief active agents in the utilisation of the glycogen. In them the glycogen is converted first into glucose, and afterwards into carbon-dioxide and water. The share of the liver in the process of sugar destruction is purely passive—not active. The liver is merely a storage and a distributing centre for the sugar of the body.

Fate of Glycogen of the Liver.—Two views are held at the present time with regard to the fate of the glycogen stored in the liver. Both agree that the glycogen ultimately leaves the liver, an obvious deduction, otherwise the stored carbohydrate would represent so much valuable food stuff permanently lost to the body ; they differ, however, as to the form in which the glycogen leaves the organ. According to the view of Claude Bernard, the formation of dextrose from the stored glycogen is a constant function of the liver, and a true function of that organ, not merely a post-mortem phenomenon. Sugar is stored in the liver as glycogen in order to avoid flooding the organism with material at a time when it is not needed, and when it cannot be dealt with in large bulk, and further, when it would merely be excreted by the kidneys. Muscles use sugar in the performance of muscular work; sugar is the main source of the energy phenomena of the body, for heat and work are to a great extent ultimately derived from sugar oxidation. As the muscles and the other tissues use up their sugar content, more must be supplied them. This necessary further supply is furnished by the resolution of a certain amount of the stored glycogen into sugar, and its transmission by the blood stream to the required destination. On this point of view, liver, muscles, and kidneys together form a delicately adjusted mechanism for the distribution and utilisation of sugar. They together maintain the sugar content of the blood of the systemic circulation at a constant level.

The second view, that of Pavy, is opposed to Claude Bernard's. Pavy believes that the formation of sugar from liver glycogen is entirely a post-mortem phenomenon, and that no such change occurs during life. During life the glycogen of the liver does undergo alteration, but not into dextrose. It is transformed continuously into fat, and *helps* to build up protein. There certainly is some support for this view, seeing that fat is certainly formed from carbohydrate; but, on the other hand, there are equally strong, if not stronger, arguments in favour of Claude Bernard's view. A particularly powerful experimental observation in favour of this view is the following: the percentage of sugar in the blood remains constant in the normal starved animal, but, if the liver is extirpated, the percentage of the sugar in the blood gradually diminishes. This would seem to show that it is the production of sugar in the liver which maintains the constant percentage of sugar in the blood of a starved animal; and this, taken in conjunction with the fact that the glycogen of the liver diminishes during starvation, would seem to show that the sugar is produced from the liver glycogen.

It seems quite possible, however, that a combination of the two views will help towards a correct explanation. Accordingly, the storage of glycogen in the liver will serve two purposes:—

1. It will form a convenient mode of sugar storage, from

which the sugar can be easily enough re-formed, and thus rendered available for energy purposes in the organism.

2. It will form a fund upon which the liver can draw in order to transform sugar into fats and help to build proteins, processes which are doubtless, in all probability, carried out in the liver.

Much light is thrown upon the whole question of sugar metabolism, including glycogen formation and the relation of sugar to other materials in the animal body, by the consideration of "Experimental Glycosuria."

EXPERIMENTAL GLYCOSURIA.

Diabetic Puncture.—Claude Bernard was the first to demonstrate that certain neural lesions, artificially produced, resulted in the production of sugar in the urine. Since his time the experiment, as he described it, has been repeated on various animals, and with the same result. It is usually known as Claude Bernard's piqûre or diabetic puncture experiment. The animal (usually a rabbit) is placed on its abdomen, and the point of a trocar is placed upon the external occipital protuberance, and pushed through the skull in the direction of the basilar portion of the occipital bone. The instrument passes through the cerebellum and into the medulla oblongata, where are the nuclei of the columns of Goll and Burdach and the floor of the fourth ventricle of the brain, all of which are chiefly affected. Two hours after the experiment sugar appears in the urine, and the elimination of sugar via this path is continued for some time, the actual period depending upon the animal employed, and upon its nutritive condition at the time of the experiment. Not only is there a glycosuria, but, as Claude Bernard further showed, this condition is merely the result of an accompanying hyperglycæmia; that is to say, a percentage of sugar in the blood exceeding 0·15. The hyperglycæmia is due to increased production of dextrose from the glycogen which is stored in the liver; the dextrose passes out by the hepatic veins into the general circulation. It would seem, then, that the glycogen function of the liver is in some way under the control of the nervous system; and further research has demonstrated the course of the nerves involved in this control. If, in an intact animal, one of the vagi is cut, and the central end stimulated, dextrose immediately appears in the urine, and continues to be excreted in this manner for as long as three-quarters of an hour after the cessation of the stimulation. Following each stimulation, a transitory glycosuria appears. On the other hand, stimulation of the peripheral end of the divided vagus is without effect on the sugar content of the organism. It may therefore be assumed that the vagi must be, in this connection, afferent nerves, and that the glycosuria is produced reflexly by the stimulation of some centre—a *diabetic centre* in the medulla. The effect of the "diabetic puncture" is through *direct stimulation* of the cells of the "diabetic centre." Stimulation of the upper cut end of the depressor nerve, and similarly with the spinal nerves (*i.e.* the sciatic nerve), also has much the same effect. The efferent path is through the spinal cord; the fibres passing out of the cord through the upper thoracic nerves and reaching the liver via the splanchnic nerves. If the splanchnic nerves are previously cut, or nicotine painted on the upper thoracic ganglia so as to block the nervous impulses, stimulation of the diabetic centre does not result in glycosuria. In these circumstances the nervous impulses started in the diabetic centre fail to reach the liver.

The exact rôle of this reflex in the sugar economy of the body has never been completely elucidated, although Pflüger has proposed an ingenious speculation. He points out that muscles in contraction stimulate the muscle spindles contained in themselves (particularly in their tendons). This stimulation, he assumes, reflexly stimulates the "diabetic centre" in the medulla, and thus causes an elimination of the liver glycogen from that organ as dextrose. The dextrose thus produced passes into the systemic blood from the hepatic vein, and is utilised in replacing the sugar used up in the performance of muscular work. One fact concerning carbohydrate metabolism, about which there is no doubt, is that sugar is the *first* and *most important* source of muscular energy.

In this type of glycosuria it is important to remember that there is absolutely no disturbance of the glycogen contained in the muscles of the body. It is essentially a nervous disturbance affecting the liver glycogen only. The puncture, too, is effective only when the liver contains glycogen. It is quite ineffective in an animal whose stores of liver glycogen have been depleted from any cause, either from previous starvation or from excessive muscular work.

Clinically, certain cases of glycosuria appear to have been traced to disturbances in the central nervous system, such as injury to the brain and the upper part of the spinal cord, tumours in the fourth ventricle, and cerebellar hæmorrhage (Langdon Brown). These lead to an alteration of the "glycogen retention" function of the liver, possibly by irritating the diabetic centre or the nerve fibres in the cord which carry down the impulses from that centre.

Other types of glycosuria can be brought into line with this "diabetic puncture" type.

Injection of Salts or Vascular Glycosuria.—If a solution of certain strength of sodium chloride is injected into a vein of an animal, glycosuria is produced. This is due to direct stimulation of the medullary centre, for it is produced very much more quickly and with greater certainty when the salt is injected into a vessel going directly to the brain, than when into a vessel of different direction (Martin H. Fischer). Also, like "puncture diabetes," the effect is produced only if the animal experimented upon has glycogen stored in considerable amount in its liver. An instructive illustration of the antagonistic effects of sodium (Na') and calcium (Ca'') ions can be demonstrated in this experiment. If calcium chloride, or any other soluble ionisable salt of calcium, is injected into the animal during the time that glycosuria persists from the previous sodium salt injection, the glycosuria is cut short. It reappears only when more sodium chloride is injected; and similarly, further calcium chloride injection again abolishes the resulting glycosuria.

Injection of piperine and other drugs, especially anæsthetics, is often followed by glycosuria. This appears to be due to the resulting dyspnœa, for it does not appear if at the same time that the drug is administered oxygen is supplied (Underhill). Perhaps such glycosurias, which are always accompanied by, and therefore due to, hyperglycæmia, may be due to stimulation of the medullary centre, which is in close proximity to the respiratory centre.

In the forms of glycosuria already described it is evident that in no sense of the term is carbohydrate metabolism disturbed. The difficulty lies, not in the capacity of the organism to utilise and to burn up sugar, but there seems to be an increased production of dextrose from the previously stored glycogen of the liver, hence the hyperglycæmia with the resulting glycosuria. Such forms cannot be considered as grave, deep-seated abnormalities in the metabolic processes. They stand in the closest relationship to such forms of glycosuria as *alimentary glycosuria*. This is a very simple type of glycosuria due to ingestion of too large amounts of sugar. Thus if a very large quantity of dextrose is given to an animal, or injected into the blood of an animal, glycosuria very quickly supervenes. Too much sugar is carried to the liver, via the portal vein, for that organ to have adequate time to store it up. Consequently, some of the dextrose eludes the grasp of the liver cells and passes by them into the hepatic vein. The sugar percentage of the systemic blood is raised, and the kidneys, acting like a filter, endeavour to remove this excess with consequent glycosuria. For every carbohydrate there is what Hofmeister termed the "assimilation limit." The animal utilises all the particular carbohydrate supplied, so long as the quantity lies below this particular limit; if the quantity ingested exceeds this value, a large amount of it escapes the liver and finds its way into the urine. It is obvious, in the case of such a polysaccharide carbohydrate as starch, that the assimilation limit must be higher than with dextrose, for the starch must be first resolved by the action of the amylolytic enzymes (ptyalin of the saliva and amylopsin of the pancreatic juice) into the simple monosaccharide, dextrose, before absorption. This reaction takes time, so that part of the sugar resulting from the starch hydrolysis may have been absorbed and assimilated even before the remaining portion of the starch has undergone any appreciable hydrolytic cleavage.

PHLORIDZIN GLYCOSURIA.

If phloridzin is injected into a vein of an animal glycosuria almost immediately results. The same result is obtained even when the animal used contains no glycogen stored in its liver, and even, indeed, if it is in a state of starvation. Moreover, when all the glycogen stores of the body have been given up, owing to previous injection of the drug, injection of the drug still brings about glycosuria. Certainly, in this case the dextrose must have a source other than that of the sugar of the animal; similarly, it does not come from the phloridzin itself. Phloridzin certainly is a glucoside, a fact which has led Pflüger to assume that the sugar, which appears so quickly in the urine after phloridzin injection, might possibly be split off from the phloridzin itself, but the small amount of carbohydrate, contained in the injected phloridzin, does not suffice to explain the large amount of urinary sugar, and further, injection of phloretin, the glucose-free component of the phloridzin molecule, also causes glycosuria. It is peculiar, too, that injection of the drug into the renal artery causes the appearance of dextrose in the urine excreted by that kidney more quickly than in that of the other side (Zuntz) (*vide* p. 443). In phloridzin diabetes there is no hyperglycæmia. It is supposed that the appearance of the sugar in the urine is due to increased permeability of the kidney allowing sugar to escape. It is further obvious that this sugar must be derived from something which is not sugar; for, as has been stated already, it is produced even in starving animals, and when all the sugar supplies of the organism have been exhausted. It seems that its source must be protein material, and Lusk has shown that, in the glycosuria due to phloridzin, the nitrogen excretion of the urine increases, and that Minkowski's ratio $\frac{D}{N} = \frac{\text{Dextrose}}{\text{Nitrogen}}$ of the urine remained at a constant level, namely, about 3·6, after all the carbohydrate store of the body had been got rid of by the previous injection of phloridzin. This would be the case if the sugar had a constant source and was derived from protein. If all the protein, metabolised and disintegrated in the body, remaining after the formation of urea, was utilised solely for the formation of sugar, the ratio $\frac{D}{N}$ would be 7, for protein contains 52 per cent. carbon and 17 per cent. nitrogen. Urea would account for 7 grms. of carbon, for it contains 28 grms. nitrogen to 12 of carbon; the carbon unaccounted for (45 grms.) would yield 112 grms. of sugar, consequently $\frac{D}{N} = \frac{112}{17} = 7$. Lusk's value would indicate that a little more than half of the protein metabolised had been converted into dextrose. From a consideration of the components of the protein molecule it is obvious that the sugar might come from two sources :—

1. From that carbohydrate radical which is present in many of the proteins, namely, glucosamine, an amino derivative (NH_2) of glucose. Its relationship to glucose is shown thus :—

$CH_2OH.(CHOH)_4.CH(OH).CHO$ . . Glucose.
$CH_2OH.(CHOH)_4.CH(NH_2).CHO$ . . Glucosamine.

This origin seems scarcely probable; for the amount of glucosamine contained in the different proteins apart from the mucins and mucoids (the glyco-protein group) is very small, and is very far from explaining the existence of the large amount of sugar which appears in the urine. It is possible, however, that it may play some *small* part in the production of this sugar.

2. From certain of the amino-acids. Certain of these bodies stand in very close relation to sugar and its derivatives. One of these is alanine. This is the amino derivative of propionic acid, as seen by the following constitutional formulæ :—

$CH_3.CH_2.COOH$ . . Propionic acid.
$CH_3.CH.NH_2.COOH$ . . Alanine.

If the NH_2 group is replaced by OH, lactic acid is produced.

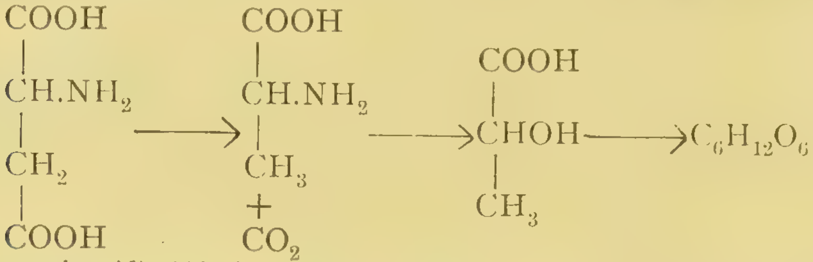
$CH_3.CH.OH.COOH$ . . Lactic acid,

and lactic acid stands in the closest relationship to the carbohydrates; in fact, it can be obtained from sugar in the lactic acid fermentation :—

$$C_6H_{12}O_6 = \underset{\text{(Lactic acid)}}{2C_3H_6O_3}$$

It is possible that the reverse change may take place.

If alanine is given to an animal suffering from "phloridzin diabetes" there is an increase of sugar excreted in the urine; and even in the normal animal alanine administration leads to an increase of glycogen in the liver. Similarly, aspartic acid (amino-succinic acid) given to an animal suffering from "phloridzin diabetes" causes an increase in the sugar excretion. The chemical relationship of aspartic acid to glucose is thus shown:—



$$\begin{array}{c} COOH \\ | \\ CH.NH_2 \\ | \\ CH_2 \\ | \\ COOH \end{array} \longrightarrow \begin{array}{c} COOH \\ | \\ CH.NH_2 \\ | \\ CH_3 \\ + \\ CO_2 \end{array} \longrightarrow \begin{array}{c} COOH \\ | \\ CHOH \\ | \\ CH_3 \end{array} \longrightarrow C_6H_{12}O_6$$

(Aspartic acid) (Alanine + CO_2) (Lactic acid) (Sugar)

It appears that in "phloridzin diabetes" the kidney itself is capable of effecting this change, but observations of a different nature have shown that the liver of the normal animal is also capable of carrying out this change. An animal which has been starved for one or two days, and previously to this fed upon milk only, is given strychnine in sufficient quantity to produce convulsions (artificial respiration must be maintained). After the convulsions have continued for five hours chloral is given, and the animal falls into a deep sleep. If it is killed within twelve hours after the convulsions, and the liver examined, it is found to contain no glycogen, but if killed after the elapse of that time glycogen is present, and the amount steadily accumulates with time (Frentzel). In order to investigate the action of any food stuff upon glycogen formation in the liver, it is only necessary to administer the food material with the chloral, and for the animal to be killed within twelve hours after the chloral administration. Feeding experiments have for a very long time (since Claude Bernard) been thought to prove that the liver was capable of utilising protein in the formation of glycogen, a necessary intermediate stage in the process being, of course, the formation of glucose from the protein. The observation above demonstrates its truth.

The following are other amino-acids which stand in close relationship to alanine, and therefore to lactic acid, and could very well share in the formation of glucose, and consequently in that of glycogen:—

$CH_3.CH(NH_2).COOH$	Alanine.
$CH_2.OH.CH(NH_2).COOH$	Serine.
$\left\{\begin{array}{l} S.CH_2.CH(NH_2).COOH \\ S.CH_2CH(NH_2).COOH \end{array}\right.$	Cystine.
$SH.CH_2.CH(NH)_2.COOH$	Cysteine

Similarly, the bodies tryptophane (indole-amino-propionic acid), phenyl-alanine, tyrosine (oxyphenyl-alanine), and histidine (imidazole-amino-propionic acid), which all contain alanine or amino-propionic acid, all stand in close relationship to lactic acid ($CH_3.CH(OH).COOH$ or $C_3H_6O_3$).

When pancreatic diabetes is being considered, it will be shown that certain of these amino-acids, when administered, cause an increase in the amount of sugar excreted in the urine.

Chemically, then, it is extremely probable that protein may serve as a source of sugar; and experimental support is provided in experiments upon dogs, in which glycosuria has been induced by complete removal of the pancreas.

PANCREATIC DIABETES.

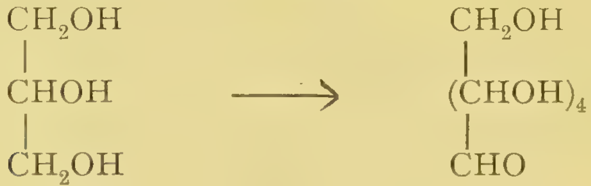
Extirpation of the entire pancreas of an animal is followed by hyperglycæmia and consequent glycosuria. If, however, a small piece of the pancreas is left *in situ*, or a piece of pancreas is grafted into the animal from which the pancreas has been previously removed, so long as this particular piece of pancreas retains its vitality no glycosuria occurs.

This type of glycosuria has been recognised as approximating closest to the condition in diabetes mellitus. The hyperglycæmia is not due to defective power of oxidation, for such substances as benzene, glycuronic acid, and similar bodies are easily and completely oxidised by the organism, although these substances, in normal circumstances, are much more difficult to deal with than glucose. The whole inability of the organism to utilise sugar appears to lie in the fact that the organism appears to have lost the power of preparing the sugar for oxidation. It is believed that, under normal conditions, it is the pancreas which influences this process by the production of an internal secretion. This secretion is distributed by the blood stream, and in some way influences the course of normal carbohydrate metabolism. Thus, in the case of the muscles, it appears from the observations of Cohnheim that, whilst the muscle juice is incapable by itself of destroying sugar, if to the muscle extract an extract of pancreas is added, combustion of sugar is immediate. The pancreatic extract itself, however, just like the muscle extract, is incapable of effecting the change.

It has been suggested that the internal secretion of the pancreas acts as an "amboceptor" by which the dextrose, supplied to the tissue, is linked on to, or adsorbed to the tissue proteins, and is then in the tissues ready to be oxidised. If this internal secretion is absent the dextrose is no longer taken up by the tissue proteins, hyperglycæmia occurs, and glycosuria follows.

The internal secretion itself, it is assumed, is a product of the activity of the cell islets of Langerhans, which occur scattered throughout the interacinar connective tissue of the pancreas. At the same time it seems, from some observations made by Dale, that the islets are merely stages in the life history of the individual acini (*vide* p. 109).

By experiments upon animals, from which the pancreas has been removed, it has been shown that injection of alanine, tyrosine, aspartic acid, and other related amino-acids leads to the formation of glucose and to its excretion in the urine. Similarly, another interesting relationship is the fact demonstrated first by Lüthje, that glycerin similarly gives rise to an increase of the sugar excreted. This is interesting because, in the first place, sugar has been artificially synthesised from glycerin (E. Fischer); and, in the second, it has been shown that, besides proteins, fats also, from their glycerin component, can give rise to sugar and glycogen—



$$\begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} \longrightarrow \begin{array}{l} CH_2OH \\ | \\ (CHOH)_4 \\ | \\ CHO \end{array}$$

(Glycerin) (Dextrose)

Another point found, not without practical importance, is that, although there is such profound disturbance of carbohydrate metabolism, yet it appears that the organism is still capable of utilising fructose, and even of storing it up in the liver as glycogen, but whether as ordinary glycogen or a different kind is not known. Fructose, like dextrose, is a monosaccharide, but whereas dextrose is an aldehyde sugar (aldose), fructose is a ketone sugar (ketose). It at least seems certain that the fructose does not undergo a preliminary change to dextrose, otherwise it would cause an increased excretion of dextrose in the urine.

Glycosuria may also be produced by the administration of epinephrin (adrenalin) and thyroid extract. How these substances act has not been definitely determined. It has been suggested, however, that the glycosuria which follows the administration of adrenalin is due to interference with the internal secretion of the pancreas, by which dextrose is not adsorbed to the tissue proteins. Hyperglycæmia occurs and glycosuria follows.

GENERAL REVIEW OF CARBOHYDRATE METABOLISM.

The sugar absorbed by the cells covering the intestinal villi is carried in the portal vein to the liver, some of the dextrose which is immediately required by the tissues is allowed to pass on; the major portion of the sugar, however, is stored as glycogen. The glycogen-storing function of the liver is under nervous control, a fact proved by the "diabetic puncture" experiment, or by stimulation of the medullary centre by means of drugs or normal saline. If, from any cause, the liver cells are in a state of impaired vitality, it is no wonder that a mild form of glycosuria ensues; because the sugar, instead of being stored in the liver as glycogen, escapes in excess into the systemic blood, and raises the percentage of sugar in the blood above the maximal limit of 0·15 to 0·2 per cent., with consequent hyperglycæmia and glycosuria. Similarly, alimentary glycosuria is easy to understand, because here again too much sugar is passed to the liver for it to deal with it adequately.

Dextrose is taken to the muscles, where it is assimilated, it may be adsorbed to the tissue protein, and it is possible that the internal secretion of the pancreas is all important in stimulating the tissues to take up the dextrose. Extirpation of the pancreas is followed by intense glycosuria lasting until the death of the animal, in which it is obvious that the protein and fat supplies of the organism, besides its carbohydrate supplies, must be called upon to furnish the excreted sugar. Similarly, phloridzin injection causes a severe glycosuria, although it apparently differs from all other types of glycosuria in being due to some disturbance of the kidney, and most probably the cubical cells lining the convoluted tubules.

To sum up the results of observations upon animals, experimental glycosuria may be considered under two headings, namely—

1. Glycosuria resulting from excess of sugar in the blood (hyperglycæmia). This may be produced by—
    - (*a*) Overfeeding with, or the injection of, dextrose.
    - (*b*) Diabetic puncture.
    - (*c*) Injection of strong solution of NaCl.
    - (*d*) Complete removal of the pancreas.
2. Glycosuria, without hyperglycæmia, produced by—
    - (*a*) Phloridzin, or phloratin injection.

CHAPTER XXIX.

FAT METABOLISM.

A. Anabolism.

THE greater part of the fat of the body is derived from the fat of the food. Fats are compounds of glycerin and fatty acid, one molecule of the trihydric alcohol being combined with three molecules of the fatty acid to form the neutral fats—triolein, tripalmitin, and tristearin, named according to the fatty acids—oleic acid, palmatic acid, and stearic acid.

$$\begin{array}{ccc} \left\{\begin{array}{l} CH_2O(C_{17}H_{33}CO) \\ CHO(C_{17}H_{33}CO) \\ CH_2O(C_{17}H_{33}CO) \end{array}\right. & \left\{\begin{array}{l} CH_2O(C_{15}H_{31}CO) \\ CHO(O_{15}H_{31}CO) \\ CH_2O(C_{15}H_{31}CO) \end{array}\right. & \left\{\begin{array}{l} CH_2O(C_{18}H_{35}CO) \\ CHO(C_{17}H_{35}CO) \\ CH_2O(C_{17}H_{35}CO) \end{array}\right. \\ \text{(Triolein)} & \text{(Tripalmatin)} & \text{(Tristearin)} \end{array}$$

In the alimentary canal the fat is resolved into glycerin and fatty acid. Should the fat be, even at the time of ingestion, in a finely emulsified form, *e.g.* milk, the gastric juice by the gastric lipase present, exerts a considerable lipoclastic action (Voltard); but more solid fat is first emulsified by the action of the bile and the pancreatic juice, and then hydrolysed by the activity of the lypolytic enzyme of the pancreatic juice. At the same time, however, the gastric juice in all cases plays a most important part in the digestion of fat, for usually the fat is administered to the animal in its original form. In this condition it is not pure fat, but is fat divided into small portions each of which is surrounded by a connective-tissue capsule. It is the function of the gastric juice to set free the fat by the digestion of this sclero-protein. The fatty acid and glycerin, set free in the small intestine, are absorbed by the cells covering the intestinal villi, and in these cells are again converted into fat. Even if fatty acid only is administered, still fat is built up in these columnar cells, the cells apparently possessing the power of forming glycerin.

It is obvious, from what has already been mentioned under glycosuria, that this glycerin might be derived, either by the removal of the amino group (NH_2) from certain of the amino-acids with transposition of the remaining elements, cp.—

$CH_3.CH(NH_2).COOH$	Alanine
$CH_2OH.CHOH.CH_2OH$	Glycerin

or by breaking up of sugar

$$CH_2OH.(CHOH)_4.CHO.$$

The fat, so formed in the cells covering the intestinal villi, is carried to the central lacteal by those lymphocytes which are present in the villi. It is transferred here to the lymphatic stream, helping to form the chyle. The chyle passes by the efferent intestinal lymphatic vessels to the receptaculum chyli, and thence by the thoracic duct to enter the general systemic blood at the junction of the left internal jugular and the left subclavian veins. Thus the fat absorbed from the intestines escapes the liver, and passes directly to the tissues. In certain neighbourhoods this fat is stored up, the chief fat depôts of the body being three in number. They are—

1. The subperitoneal fatty tissue.
2. The subcutaneous fatty tissue.
3. The intermuscular fatty tissue.

It appears that the fat itself is incapable of being transmitted, as it is, from the blood to fatty tissue; it must apparently be first transformed into glycerin and fatty acid, and these are again synthesised together to form fat in the particular organ in which the fat is destined to be deposited. The lipolytic or lipoclastic enzyme (tissue lipase) appears to be the chief agent in effecting these changes, under certain conditions producing the synthesis, and under others the analysis of the fat (Lowenhart). In the fatty tissue the fat deposited is actually laid down in the cytoplasm of the fat cells. At first only a small drop of fat is apparent, which, increasing in size, reduces the protoplasm of the cell to a mere envelope covering the fat, and containing a flattened nucleus. The fat thus deposited stands in the closest relationship to the fat ingested in the food; indeed, the fat deposited is exactly the same as the fat ingested. Thus Hofman starved a dog until all its fat stores were entirely used up, then he fed it upon bacon fat, when it was found that the fat laid down in the fat depôts of the animal was exactly the same, with regard to its various properties, as the fat administered to the animal. Similarly, rape-seed oil given to a starved dog leads to the deposition of rape seed oil in the fatty tissues (Munk).

Consequently it will be understood, from what has been stated already, that the fat of the animal is to a large extent derived directly from the fat of the food. But this is by no means the whole case. Fat is also derived from carbohydrate food material; this was shown long ago by Lawes and Gilbert, although farmers have for a much longer time known the practical importance of this fact, for they fatten their live stock by feeding it on starchy material. The actual chemical changes involved in this transformation are unknown, and so far the chemist has not been able to effect it. It may be represented empirically by the equation—

$$x\ C_6H_{12}O_6 = y\left\{\begin{array}{l} CH_2O(C_{17}H_{33}CO) \\ \mid \\ CHO(C_{17}H_{33}CO) \\ \mid \\ CH_2O(C_{17}H_{33}CO) \end{array}\right. + w\ H_2O + z\ CO_2$$

With regard to the fact that carbohydrate food material gives rise to animal fat, however, there is not the slightest reason for doubt, although it cannot be explained with our present knowledge. Perhaps the girth of the beer-drinker will bear witness to the general fact.

With regard to the origin of fat from protein food material, there is room for doubt. Physiologically, there are no definite uncontrovertible facts pointing to such a process; although from a chemical standpoint nothing can be urged against it. Indeed, it would seem quite likely that the amino-acids, by the loss of nitrogen (which is split off in the liver with the formation of urea), would yield lower fatty acids, and it would seem probable that these lower fatty acids might be easily enough built up into higher fatty acids.

Functions of the Fat.—The fat of the body, which is not only contained in the fat depôts but also disseminated through the protoplasm of individual cells, has most important functions to perform.

1. It acts as a reserve substance, much in the same fashion

as does glycogen, which the body can draw upon whenever from any cause its nutritional resources are in a precarious condition.

2. It often performs functions in a purely mechanical fashion, forming pads and sheaths for delicate organs, *e.g.* the fat of the orbit.

3. It is important in maintaining the heat of the body, for it is a non-conductor of heat, and thus, forming as it does an entire subcutaneous covering for the body, it is important in regulating the heat loss from the body.

4. But much more important than these functions is the part which fats and fat-like bodies (lipoids) play in the processes of the cell. Bang has maintained that the lipoid (*e.g.* lecithin) components of the protoplasm of the cell must be regarded as of equal significance with proteins in the performance of the functions of life. Certainly they appear to play most important functions in the formation of cell membranes (particularly of the red blood corpuscles), and also in the production of narcosis. According to the Meyer-Overton theory of the action of narcotic drugs, these substances exert their action owing to their solubility in lipoid materials and their power to permeate into the nerve cells, a property dependent upon the characteristic of these drugs mentioned above.

B. Katabolism.

The katabolism of the fats is a subject about which little is known at present, but about which during recent years some interesting facts have come to light. The final products of the oxidation of fat are carbon-dioxide and water, substances which are excreted by the lungs and kidneys respectively. It seems that the fatty acids are first broken down into unsaturated fatty acids, which are then further destroyed with the production of carbon-dioxide, water, and other lower unsaturated fatty acids, and so on, until finally the acid is completely converted into carbon-dioxide and water. The liver seems to play a most important part in this process. These observations stand in the closest relationship to some previous isolated facts which were observed in diabetes mellitus and other severe glycosuric conditions. It is frequently in these conditions, when death is approaching, that coma supervenes. This is apparently due to an acid intoxication (acidæmia or acidosis), the acid in this case being the β-hydroxybutyric acid. In these circumstances, β-hydroxybutyric acid and its derivatives, diacetic acid and acetone, are excreted in the urine. It was formerly thought that these substances were derived from protein or carbohydrate material, but this does not appear to be so, for in certain cases the amount of these substances was much more than could possibly have been produced by destruction of protein material. It seems certain that they are *derived from fat*, and this is supported by the fact that administration of fat to a diabetic patient causes an increase in the amount of these bodies excreted. Similarly, they appear in the urine and breath of ordinary individuals fed solely upon fat and protein. Further, during starvation of the glycosuric animal the amount of these acetone bodies is increased, and at this time the animal is living chiefly at the expense of fatty material; further administration of albumin or carbohydrate causes a diminution in the production of these bodies.

$CH_3.CHOH.CH_2.COOH$.	Hydroxybutyric acid.
$CH_3.CO.CH_2.COOH$ . .	Diacetic acid (aceto-acetic acid).
$CH_3.CO.CH_3$	Acetone, *i.e.* hydroxybutyric acid on oxidation = diacetic acid; diacetic acid $- CO_2 =$ acetone.

It seems, therefore, that these lower oxidised fats are produced in the destruction of the fat of the body, facts which support the contention previously urged that, from the higher fatty acids, lower fatty acids are made by removal of hydrogen atoms with subsequent oxidation, and that the liver is the active agent in effecting these changes.

In ordinary circumstances, fat is oxidised to CO_2 and H_2O, but, as a result of defective oxidation, as it occurs in certain diseases, these intermediate acids, such as β-hydroxybutyric acid, diacetic acid, and acetone, are produced and are eliminated in the urine. Tissue autolysis is due to certain intracellular enzymes, and proceeds more rapidly in fasting than in properly fed tissues. In starvation the fats are chiefly drawn upon, but the proteins too undergo autolytic changes. The result of this is that fatty acids are set free, and if oxidation is deficient, so that CO_2 and H_2O are not finally produced, β-hydroxybutyric acid and diacetic acid are found in the blood, and the diacetic acid and acetone are excreted in the urine.

In relation to fat katabolism, it must be remembered that fats give rise to sugar in the body,—at any rate in the glycosuric organism. Indeed, Pflüger maintains that never in any circumstances does protein give rise to carbohydrate, but it is the fat of the body which gives rise to this material.

CHAPTER XXX.

MUTUAL RELATIONS OF PROTEINS, FATS, AND CARBOHYDRATES.

It is practically impossible to consider the metabolism of any one of the individual constituents of the body apart from the others, for the metabolism of all these different materials is actually bound up into a co-ordinate and indivisible whole. With regard to the proteins, it is obvious that in the animal it is impossible for this substance to be formed from anything else than protein. True enough, the animal can build up, by the agency of the reversed action of its various proteoclastic intracellular enzymes, protein material from the products of proteolysis, but it is only from the products of proteolysis produced by the action of trypsin and erepsin. The animal organism cannot build up proteins from a simple mixture of amino-acids (Hansen and Henriques, Loewy, Abderhalden). Probably it is necessary in all cases that a polypeptide, such as results from peptic and tryptic digestion (Abderhalden and Fischer), should be left, upon which the enzymes of the individual tissues can commence their building operations. It is clear, therefore, that the tissues cannot build up protein from carbohydrate and fat. That which absolutely militates against such a hypothesis is that the element nitrogen is absent from such materials, and the animal organism is absolutely incapable of utilising nitrogen of the atmosphere or nitrogen of inorganic compounds. Consequently, in the animal body all protein is derived from protein. On the other hand, it is obvious that proteins, after the loss of their nitrogen as urea, and of their sulphur as "neutral sulphur" and sulphates, may very possibly give rise to carbohydrates and fats. The question of the origin of carbohydrate from protein under the title of glycosuria has been dealt with, and it has been shown how the chemical composition of certain of the individual amino-acids, not only supports such a hypothesis but renders it practically certain. Alanine and the alanine derivatives—tyrosine, phenyl-alanine and histidine, also serine, cystine, and aspartic acid, all stand in the closest relationship to lactic acid, a body closely related chemically to dextrose.

On the other hand, with the question of the origin of fat from protein, there still remains an element of uncertainty. Some observations have been brought forward which seemed to support this view. For example, it has been repeatedly observed that, under certain pathological conditions (phosphorus poisoning, fatty degeneration of the liver), fat may appear in the protoplasm of the individual cells, and ultimately apparently replace the whole of this protein material. According to one view of the change, this fat is derived directly from the protein, and furnishes absolute proof of the origin of fat from protein. But this explanation has been repeatedly denied, and indeed at the present time it is almost an accepted conclusion that this fat so deposited is not derived from the protein of the cells at all. It is fat which has been transported from other parts of the body, and, so to speak, dumped down in the tissue. Other observers, whilst denying the origin of fat from protein, do not accept that the so-called "fatty degeneration" is due to transported fatty material, but maintain that the fat which appears in the cells, and which can in this condition be so readily demonstrated, merely represents the fat present in that particular tissue, which was hidden before, but has now made itself apparent. It certainly is an established fact that organs like the kidneys, when examined histologically, which under normal conditions appear to contain little or no fat, yet, when examined chemically, give evidence of a considerable amount of fat present.

Observations of a similar character upon other organs have shown that, although fat cannot be demonstrated histologically, yet chemical analysis demonstrates its presence.

Although it seems an established fact that protein can give rise to carbohydrate material (although it must be remembered that so critical an observer as Pflüger doubts this statement), it must be regarded as a question still *sub judice* as to whether fat can similarly arise from protein.

The mutual relation of fat and carbohydrate has already been dealt with; so that it is sufficient to repeat that fat, at any rate the glycerin component, and very possibly also the fatty acid radical, can give rise to dextrose, also that carbohydrate is a fat former.

CHAPTER XXXI.

THE INORGANIC SALTS.

THE chief inorganic salts present in the body are the chlorides, phosphates, sulphates, carbonates of sodium, calcium, magnesium, potassium, fluoride of sodium, and the element iron, which is dealt with under the heading hæmoglobin.

These salts play a most important part in the economy of the organism. First of all, they are absolutely necessary to maintain the osmotic pressure in a constant condition. This is most important, for alterations in the osmotic pressure of the plasma, or of the cells, are accompanied by serious disturbances, which may, in fact, ultimately lead to the death of the animal. This, however, is not the only function of these salts, for each in addition has important specific functions to perform. That this must be so is at once apparent when it is remembered that, in the cells, potassium phosphate is the most abundant salt, in the plasma, sodium chloride; yet it is impossible to successfully replace the potassium of the cell by sodium, or the phosphate by chloride, without untoward results. The effects of these different elements will be dealt with separately.

The Sodium Ion.—Sodium is essential for the preservation of the irritability of the tissues, particularly muscle tissue. If a muscle is immersed in an isotonic solution of sodium chloride it retains its irritability for some time, and indeed its irritability may be maintained to such an extent that, after about one hour or so, it commences to enter into rhythmical contractions. Similarly, it has been stated that injection of sodium chloride into the circulation of an animal causes glycosuria, because of the stimulating action of the salt upon the "diabetic centre" in the medulla.

The Potassium Ion.—This acts in the reverse direction to the sodium ion, since it promotes muscular relaxation.

The Calcium Ion appears to exert an action also the reverse of that of the sodium ion. It seems to combat the effect of the sodium, which promotes irritability, and it also checks the glycosuria caused by the injection of sodium chloride.

In the clotting of milk, as it takes place in the stomach, soluble calcium salts have an important action, since they convert the soluble casein, which has been produced by the action of the rennet enzyme upon calcium caseinogenate, into insoluble casein or caseate of calcium, which is the basis of the curd.

In blood-clotting the calcium ions appear to activate the thrombokinase and so the inactive thrombogen is converted into active thrombin or fibrin enzyme. The time required for blood-clotting to occur may be estimated by drawing the blood into a capillary tube and watching the process. If, in an individual, it is found that the blood clots too slowly, soluble calcium salts may be given; if the blood clots too quickly, the blood may be partly decalcified by administering sodium citrate. It is possible, therefore, that a milk diet may predispose to thrombosis, in virtue of the large amount of soluble calcium salts which it contains. This may be counteracted by the addition of citrate of soda to the milk. According to Martin, citrate of soda acts by forming a double salt with the calcium, which is available neither for the curdling of the milk nor for the clotting of the blood. The influence of calcium ions upon the rhythm of the heart is noted in the section dealing with the heart.

Magnesium salts appear to favour inhibitory processes in the body, "the subcutaneous or intravenous injection of magnesium salts causes general anæsthesia with paralysis, in which the spinal reflexes are abolished and the arterial blood pressure lowered." In this inhibitory action, magnesium seems to be antagonistic to soluble calcium salts, which apparently are activators.

The importance of the action of these salts is at once demonstrated by some experiments of Loeb, who has shown that it is possible to get artificial pathogenesis of annelid eggs by placing them in a solution of sea water to which potassium nitrate or chloride has been added. The eggs develop naturally.

Similarly it has been shown that, if an animal is deprived of inorganic salts only, it lives very little longer than if subjected to complete starvation.

SECTION IX.

ANIMAL HEAT—THE SKIN.

CHAPTER XXXII.

ANIMAL HEAT.

THE heat which is produced in the body may be regarded as a by-product. It is the result of oxidation processes which occur during life. From the point of view of body temperature, animals may be divided into two classes :—

1. **Poikilothermal Animals** (the so-called "cold-blooded animals") are those of which the temperature varies directly with the surrounding medium; the temperature of the animal is, however, *just* above that of the surrounding medium. In such animals there appears to be no well-adjusted heat regulating mechanism, as exists in the higher types. This class of animals includes the invertebrates, reptiles, fish, amphibians, embryo birds, and embryo mammals.

2. **Homoiothermal Animals** (generally named "warm-blooded animals") have a body temperature which, in normal circumstances, remains fairly constant. The advantage of having such a constant temperature is that it makes an animal more independent of its surroundings.

The temperature of man in health is between 98° and 99° F. (36°·5–37°·5 C.). In most mammals the temperature varies between 37°·5 and 39°·5 C., but birds have a higher temperature, or about 42° C. The temperature of man varies slightly under the following conditions :—

1. *The Part of Body where recorded.*—The temperature of the skin is lower than that of the mouth or rectum. The temperature of the blood from the liver, where metabolism takes place very actively, is higher than in other parts of the circulation. During its passage through the lungs the blood loses heat.

2. *Age.*—As a rule the temperature of the child is higher than that of the adult, and that of the adult higher than that of the old person.

3. *Time of Day.*—The temperature is highest between 5 and 6 p.m. (about 37°·5 C.), and lowest about 3 a.m. (36°·8 C.); at this time metabolism is at its lowest ebb. In persons who work at night and rest during the day, the daily rhythm of temperature may become changed: the maximum temperature being reached at 3 a.m., and the minimum at 6 p.m.

4. *Exercise.*—Muscular exercise, as a rule, causes a temporary rise of body temperature, about 0·5° C. Pembrey states that during muscular activity the temperature of the body of a healthy man may rise as high as 102° F. This may be observed if the temperature is taken in the rectum or stream of urine. The heart responds to this rise of temperature by contracting more quickly.

5. *Inanition* causes a fall in the body temperature.

SOURCE OF ANIMAL HEAT.

The chief source of heat production in the body is the process of oxidation which takes place in the tissues. One great sign of life is the avidity which the tissues have for oxygen, and in this the tissue proteins are all important. They, governed by the ions of the inorganic salts in solution, adsorb oxygen, some of which appears to be utilised at once for oxidation purposes, whereas much is held loosely for future use.

No doubt heat is produced during the digestion of the food, not only in the process of breaking large into smaller molecules, but by the activity of the digestive glands which pour their secretions into the alimentary canal. Heat is also produced during the contraction of the plain muscle of the alimentary canal, which results in the peristaltic and other movements associated with digestion. Of the glands of the body, the liver, which is the largest, is the most active. The liver cells have to deal with the absorbed carbohydrates and the products of protein hydrolysis, forming and storing up glycogen and reconverting it into dextrose, forming urea, uric acid, creatinine, etc. In these activities the liver cells appear to be aided by the oxidases which help to bring about the process of oxidation. In short, it may be said that metabolism takes place most actively in the liver, and that the katabolic processes which occur there are a very important source of animal heat.

Heat is also produced as a result of those metabolic processes which result in the activity of the heart muscle and the muscles of respiration.

Some heat, no doubt, is produced as the result of the metabolic changes which occur in the nerve cells of the central nervous system, but the great source of animal heat is the mass of striped muscle of the body. Even when the voluntary muscles of the body are at rest they exhibit tonus, and, in order that tonus may be maintained, metabolic changes must take place in the muscles themselves. There is no doubt that as alterations of tonus occur, so the amount of metabolism and consequently heat production vary; in other words, the *tone* of the muscles is accompanied by chemical changes, and therefore by the production of heat. In cold countries, where more animal heat is required to be produced, the muscles are toned up; on the other hand, in hot countries, where less animal heat is required to be produced, the muscles become slack and flabby. If the nerves which are distributed to the leg of a dog, which is already at rest, are cut, the metabolic changes which occur in the part are diminished. When the muscles are actively contracting, such as occurs during exercise, increased oxidation (katabolic changes) occurs in the muscles, the result of which is an increased production of energy, and heat is also evolved.

The adsorbed carbohydrate is the first substance in the body to become oxidised, then the adsorbed fat. In normal circumstances, with a plentiful supply of food, the tissue protein does not undergo oxidation; but, as the result of the "wear and tear," some of the protein becomes broken into simpler substances, such as amino-acids and ammonia, and these are eventually oxidised in the liver to form urea. It is found that there is no *immediate* increase of nitrogen output from the body following muscular work, provided that the individual starts with stores of energy in the form of glycogen, dextrose, and fat sufficient to prevent any demand being made upon the protein of his tissues to supply the energy which is required for the performance of that muscular work. Muscular work, in the case of man and other warm-blooded animals, is accompanied by a rise of the internal temperature; this is due to increased oxidative changes, and therefore an increased production of carbon-dioxide. Haldane and Priestley have shown that muscular work causes a rise in the tension of carbon-dioxide in the alveoli of the lungs. As a result breathing becomes deeper in order that this waste product may be quickly eliminated from the lungs, and presumably, therefore, from the blood which is in the lung capillaries. The intake of oxygen and the output of carbon-dioxide are immediately increased by muscular exercise, and, under normal conditions, are proportional to the physiological work done.

The indirect source of animal heat is the food which is taken into the body to be digested, absorbed, and assimilated. Each proximate principle of the food has its own physiological heat value. The physical heat value of a food may be obtained by completely burning (oxidising) it in a *bomb calorimeter*. A known weight of the food is placed in a bomb, which is immersed in a known volume of water at air temperature, contained in a brass vessel. The whole is enclosed in an ebonite casing which is a non-conductor of heat. The bomb is connected with a cylinder of oxygen, which is under high pressure. The food which is in the bomb is oxidised, or ignited, by means of an electric spark. The products of combustion pass away from the bomb through a special delivery tube, which passes through the water in the vessel. During the combustion the water around the bomb is kept in motion by a stirrer driven by a motor. When the combustion is complete the rise in the temperature of the water is observed. The rise in the temperature of the water multiplied by the weight of the water gives the amount of heat expressed in calories. One small calorie, or unit of heat, is the quantity of heat necessary to raise 1 grm. of water through 1° C. The amount of heat produced by food burned in a calorimeter, *i.e.* the "physical heat value," is greater than the heat produced by the same amount of food "burned" in the body, *i.e.* the "physiological heat value." That this is especially the case with the proteins will be understood from the following fact: proteins do not undergo complete combustion in the body; each grm. of protein yields about one-third grm. of urea, and this has a heat value of its own. "Any difference between the physical and physiological heat values of fat and carbohydrates may be neglected, provided the fat and carbohydrate in the digested food is completely absorbed" (Halliburton).

The physiological heat values of the different proximate principles of the food are as follows:—

One grm. of protein represents 4100 small calories.
One grm. of fat represents 9300 small calories.
One grm. of carbohydrate represents 4160 small calories.

In this way the heat value of a diet may be readily calculated.

The actual amount of heat produced in the body may be ascertained by estimating the amount of heat given off from the body. This is done by using the *Atwater-Benedict calorimeter*. This instrument consists of a room with non-conducting walls. Coils of water pipes, fitted with metal discs, pass through the room. As heat is produced in the room it is taken up by the metal discs, and communicated to the water in the water pipes. The temperature of the water as it enters the calorimeter is ascertained, also the temperature of the water as it leaves the calorimeter. The amount of water which passes through the pipes, multiplied by the rise in temperature of the water, indicates the amount of heat given off from the individual in the calorimeter.

The amount of food ingested and oxygen used by the individual may be calculated. By measuring the urine and fæces passed by the individual, and the amount of CO_2 given off by taking it up by soda lime, and the water got rid of in the expired air by taking it up with H_2SO_4, the amount of carbon, hydrogen, and nitrogen given out by the individual may be calculated. In this way the amount of protein, fat, and carbohydrate actually metabolised may be ascertained.

The heat produced in the body is discharged in the following way:—

Radiation, evaporation, convection, and conduction from the skin, 80 to 87 per cent.

Warming water in the food, expired air, fæces, and urine, 13 to 20 per cent.

Only about 7 per cent. is represented by external mechanical work.

From experiments it has been found that the principle of the conservation of energy holds good in the living body. It is found that, if an animal is doing *no* external work, and is not gaining or losing in weight, the potential energy of the food (expressed as its heat of combustion or physical heat value) is equal to that of the heat given off from the body + that of the urine and fæces + that produced by internal work (contraction of the heart, contraction of the muscles of respiration, muscle tone, etc.). It is found also that, if an animal is *doing* external work, and is not gaining or losing weight, the potential energy of the food is equal to that of the heat given off + that of the urine and fæces + that produced by internal work + that of the external work. The law of the conservation of energy shows that, without an adequate supply of energy in the form of food, there can be no transformation in the energy of muscular work. Pembrey says: "The food must be adjusted to the work obtained from a man or beast, a truth which, if neglected, ends disastrously. A man or horse works best when well fed, and feeds best when well worked."

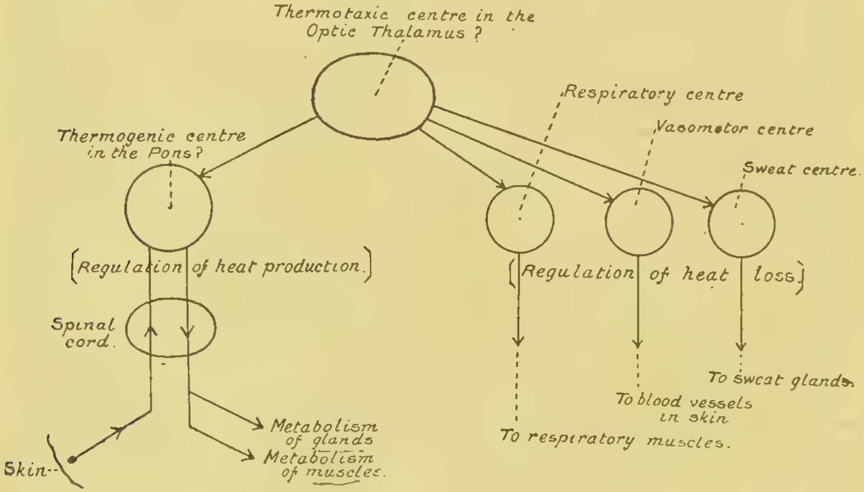


FIG. 52.

The Nervous Mechanism of Heat Regulation in Homoiothermal Animals.—The diagram shown above indicates in a general way the part the central nervous system plays in regulating the temperature of the body, by controlling the heat production and the heat loss.

1. Regulation of Heat Production.

Within certain limits the katabolic changes which occur in the glands and muscles, which result in the production of heat, seem to be reflexly controlled through the skin. If the temperature of the surrounding atmosphere becomes low, certain nerve terminals in the skin appear to become stimulated; the result of this is that afferent impulses travel up the spinal cord to the thermogenic centre, presumably present in the pons. The result is that there is increased activity of the cells of this centre, which results in efferent impulses travelling down the spinal cord to the glands and muscles, causing an increase of those katabolic changes which normally occur in these tissues. The result of this is that more oxygen is used by these tissues, and therefore that more carbon-dioxide is produced. In winter, as a rule, more carbon-dioxide is eliminated than in summer; this indicates increased katabolism, and therefore more food is required by the individual. In cold countries the inhabitants eat food rich in fat, which has a high heat value. A fairly high external temperature has the reverse effect of reflexly diminishing heat production in the tissues. In summer less carbon-dioxide is eliminated, which indicates less katabolism, and therefore less food is taken. That which is ingested, as a rule, has a low heat value. In hot countries the stable diet is carbohydrate, and a relatively small amount of protein, both of which have a low heat value. If, however, the body is exposed to undue cold over a lengthened period, the thermogenic centre is no longer able to cause increased heat production in the tissues, and the body temperature therefore falls and death finally ensues. On the other hand, if the body is exposed to undue heat, especially during exertion, "heat stroke" may occur, and the individual's temperature may become unduly raised.

In febrile conditions the rise of the body temperature is, in all probability, due to the toxins which are present in the body as the result of the disease. These act upon, and interfere with, the physiological action of the thermotaxic centre, and therefore upset the balance between heat production and heat loss. In some febrile cases the temperature may reach 107° F. or even 109° F. (hyperpyrexia). In such cases, if the temperature is not lowered within four or five hours, death may ensue from coagulation of the proteins present within the nerve cells of the brain and spinal cord.

Hæmorrhage into the optic thalamus, pons Varolii, or into the medulla oblongata, may result in pyrexia or fever, from interference with the thermotaxic or the thermogenic centres.

The heat-regulating mechanism may also be interfered with by dividing the spinal cord in the lower cervical or dorsal region, and also by the administration of curare. This drug paralyses the motor end organs in the striped muscles of the body, and consequently interferes with the thermogenic impulses reaching the muscles, and it is these impulses which appear to regulate the katabolic (oxidation) processes which normally take place in the muscles themselves. Section of the spinal cord, or the administration of curare, causes the animal to become poikilothermal. A similar change in type occurs in those homoiothermal animals which hibernate; they become poikilothermal during the period of hibernation.

Alcohol in large doses and prolonged anæsthesia paralyse the heat-regulating mechanism, so that a man deeply under the influence of alcohol resembles a "cold-blooded" animal. In these circumstances exposure to cold produces a decrease in oxidation processes, and his temperature gradually falls as a result.

2. Regulation of Heat Loss.

About 80 to 87 per cent. of the heat got rid of from the body is by means of the skin. This is provided for by two mechanisms,—the *vasomotor mechanism*, by which heat is lost by radiation, conduction, and convection; and the *sweat mechanism*, by which heat is got rid of by evaporation. These include both the visible and invisible sweat.

Radiation is most active in cold, dry air. The greater the surface of the body relative to its mass, the greater is the loss of heat by radiation.

Conduction of heat from the body takes place most readily in a moist atmosphere; hence the chilling effect of a cold and damp atmosphere.

Convection takes place only when the body is exposed to the influence of air in motion, such as a draught, or wind.

Evaporation is greatly increased after violent exertion. Some heat is always leaving the surface of the body in this way, and the larger the surface of the body the more heat is so got rid of. This explains the reason why tall persons so readily "feel the cold."

If, however, heat production is increased, as it may be, by active exercise, an increased amount of heat is eliminated from the skin by the two mechanisms, vasomotor and sweat, working in harmony. There follows vaso-dilatation, by which the skin becomes flushed with blood, and at the same time there is a large increase in the production of visible sweat.

The vasomotor and sweat mechanism of the skin, however, are independent of each other, although they usually work together. After sudden fright the skin is pale, but sweating occurs. The toxins which occur in the body as the result of scarlet fever, or the administration of atropine, cause vaso-dilatation of the cutaneous arterioles, but the sweat mechanism is paralysed in both circumstances.

The amount of heat lost by the skin is regulated, to a very considerable extent, by the variety and amount of clothing worn and the heating of rooms, etc.

About 13 to 15 per cent. of the heat got rid of from the body is eliminated in the expired air. Inspired air is warmed to body temperature, and receives warm moisture during its passage through the respiratory part of the nose, the naso-pharynx, larynx, trachea, and bronchi. Expired air is warm, and is practically saturated with warm moisture. A slight rise in temperature of the blood acts directly upon the respiratory centre. Products of katabolism, especially carbon-dioxide, stimulate to increased activity the nerve cells in the respiratory centre. In this way, as a result of active exercise producing a slight rise of temperature of the blood and an increase of the CO_2 content of the blood, there is increased activity of the respiratory centre, more rapid respiratory movements, and more heat lost by the expired air. In animals, such as the dog, which perspire but little, the respiration tract appears to be the chief means by which heat loss is regulated. After active exercise a dog breathes very rapidly, and at the same time exposes its tongue, in order that evaporation may take place from its surface.

In some of the higher mammals the heat-regulating mechanism is not "in working order" at the time of birth. In the case of puppies the power of maintaining a constant body temperature does not occur until the eyes become opened. Babies prematurely born are unable to control their heat production, and would readily die if not kept warm by special means. Babies born at full term, too, have not full power of regulating their body temperature,—at any rate, this is the case during the first week of life. Hence the importance of keeping newly born babies very warm.

CHAPTER XXXIII.

THE SKIN.

Structure.—The skin consists of two parts, the epidermis and dermis, or cutis vera.

The EPIDERMIS consists of a stratified epithelium, and the cells forming it vary in form and size from the dermis to the surface. The deep layer of the epidermis is the *stratum Malpighii* or *rete mucosum*; it lies on the papillæ and ridges produced by the dermis. The cells forming this layer have definite nuclei, and consequently they become readily stained by nuclear stains, such as logwood. In some races this layer of epidermis contains pigment granules. The cells nearest to the dermis are columnar, next to these are cuboidal cells, external to these are layers of irregular cuboidal or prickle cells. Between the cells forming the rete mucosum are intercellular spaces containing tissue fluid (lymph); there are no lymphatic vessels present in the epidermis. Ramifying between the cells are fine branching non-medullated nerve fibres forming intra-epithelial plexuses.

External to the stratum Malpighii are the more definitely horny layers of the epidermis, the nuclei of which are not very distinct, and the cells are therefore not readily stained with logwood. The cells nearest to the stratum Malpighii form the *stratum granulosum*; they are full of fine granules consisting of eleidin which they have produced from the materials supplied to them by the tissue fluid (lymph), which bathes the deepest cells of this layer.

The next layer externally is the *stratum lucidum*; here the cells are practically free from granules, their place being taken by keratin, which is formed from the eleidin. Most external to the stratum lucidum is the *stratum corneum*, the horny layer of the skin. The cells are scaly and full of keratin. This layer is particularly thick on the palms of the hands and the soles of the feet. There are no blood vessels in the epidermis.

Keratin is a sclero-protein, and consists of C.H.O.N.S, the sulphur varies from 3 to 5 per cent. If keratin is treated with acids and heated, it yields leucine, tyrosine, tryptophane, amino-acids, and hexone bases. Horn is rich in keratin, and on a shaving of horn the xanthoproteic and Rosenheim's formaldehyde reactions (Adamkiewicz reaction) can be readily performed to show that keratin contains in its molecule, tryptophane; Millon's test may also be applied, which shows the presence of an aromatic (C_6H_5) group. The sulphur of the keratin contained in horn may be detected by adding a drop of neutral lead acetate and a little caustic soda solution; on the application of heat a black colour appears, due to the formation of lead sulphide.

The DERMIS, or CUTIS VERA, consists of three layers which merge into one another. The most superficial layer is thrown into papillæ and ridges, and consists of dense fibrous tissue, and contains capillary plexuses and Meissner's corpuscles connected with medullated nerve fibres. Beneath the dense layer of fibrous tissue is a layer of loose fibrous tissue with connective-tissue cells. Deepest of all is the layer of areolar tissue and fat cells. In certain positions, such as the nipple, penis, scrotum, the dermis contains a small amount of plain muscle. That in the scrotum is known as the dartos muscle. There is also some plain muscle around the hair follicles (erector pili muscles), and a little also in the acini of the sweat glands.

The dermis is supplied with blood vessels, lymphatics, medullated and non-medullated nerves.

In the dermis, in particular regions of the skin, are situated the hair follicles, sweat, ceruminous (external auditory canal) and sebaceous glands.

Skin =
- Epidermis –
  - Stratum corneum.
  - Stratum lucidum.
  - Stratum granulosum.
  - Stratum Malpighii.
- Dermis . =
  - Dense fibrous layer forming papillæ and ridges.
  - Loose fibrous layer.
  - Areolar tissue with fat cells.

Nails are thickening of the cells of the stratum lucidum, and they rest upon the stratum Malpighii. Under the nails the dermis is thrown into longitudinal ridges, which form the nail bed. These longitudinal ridges also occur on the nails, where they may be readily seen. Nails grow from the nail groove, and the lunula at the base of the nail in this region is partly covered by the epitrichial layer of the stratum corneum. Nails develop in the fœtus at the third month, and they are covered then by the epitrichial layer of the epidermis. This becomes detached at the fifth month, leaving a free border to the nail. In the human fœtus the nails reach the tips of the fingers, but not the tips of the toes, at the end of the eighth month of fœtal life. At full term the nails project beyond the tips of the fingers, and just reach the tips of the toes.

Hairs are developed from the stratum Malpighii. Each consists of three parts,—in the centre is the medulla, which consists of round and irregular cells containing eleidin granules, pigment granules are also occasionally present. Surrounding the central medulla is the fibrous layer consisting of tapering cells closely packed; these cells are horny and pigmented. Externally is the imbricated cuticle of flattened cells overlapping one another, the free margin of the cells being outwards. At the extremity of the root is the hair bulb, into which projects a vascular papilla from the dermis. The hair is surrounded by its follicle, the layers of which correspond with the epidermis and dermis. The layers of the hair follicle are as follows, from within outwards:—

Inner root sheath corresponding with the outer part of the epidermis.	Imbricated cuticle of root sheath fitting the hair cuticle. Huxley's layer of flattened polyhedral cells. Henle's layer of oblong cells.
Outer root sheath corresponding with the stratum Malpighii.	This is supported on a fine hyaline basement membrane.
Connective-tissue layer corresponding with the dermis.	Fibrous layer. Loose fibrous tissue with blood vessels. Reticular layer.

Attached to each hair follicle is a bundle of plain muscle, the erector pili muscle. These muscles are innervated by the pilomotor nerves which leave the spinal cord by the anterior nerve roots, extending from the second dorsal nerve to the third lumbar nerve. At first the pilomotor nerves are medullated, and run into the proximal ganglia, where they form cell stations; here they lose their medulla, and emerge as non-medullated nerves. They then accompany the vaso-constrictor nerves to the skin. The hair follicles are readily responsive to adequate stimuli; this is due to the presence of a ring-like plexus of nerve fibrils around the hair follicles, within the outer root sheath, and situated just below the entrance of the duct of the sebaceous gland into the follicle.

Sebaceous Glands are formed from the stratum Malpighii, and occur most abundantly wherever there are hairs; the use of their secretion is to lubricate the hairs. Each sebaceous gland is a sacculated follicle, lined by cubical cells supported by a basement membrane and containing cubical cells in the interior. The duct runs a straight course towards the upper part of the hair follicle. The secretion (sebum) is produced by the cells which line the follicles. The fatty material contained in sebum was supposed to be produced by the degeneration of the proteins of the cells of the follicle; now it is recognised to be a true secretion produced by the cells themselves. Sebum is acid in reaction; this is due to fatty acids. It also contains isocholesterin. This substance is present in lanoline, which is made from sheep's wool. It forms crystals like cholesterin, and gives the sulphuric acid reaction. Its solutions, however, are lævo-rotatory, and it does not give Salkowski's or Liebermann's reactions (*vide* p. 50).

Ceruminous Glands are found in the skin of the external auditory canal, and in structure are similar to sweat glands, though somewhat larger. The secretion (cerumen) lubricates the fine hairs present and also the membrana tympani, and it may be, by having a bitter taste, that it deters insects, etc. from entering the external auditory canal.

Sweat Glands are developed from the stratum Malpighii, and are found all over the skin, but are particularly abundant on the palms, soles, forehead, and in the axillæ. Each gland consists of a coiled tube present in the dermis. This tube is lined on the outside by a basement membrane, on which are strands of plain muscle arranged longitudinally to the tube; internal to this are the cubical cells which line the central lumen. It should be noted that the muscle lies *between* the basement membrane and the secreting cells, and its function most probably is to squeeze out the contents of the secreting sweat tubule. The duct of the sweat gland makes a somewhat tortuous course through the dermis to the epidermis; here it is lined with a columnar epithelium directly supported upon the basement membrane. Through the epidermis the duct of the sweat gland takes a cork-screw course to the surface; here it has no wall of its own, but the wall is made up of the stratified epithelial cells of the epidermis.

SWEAT.

Sweat may be obtained by placing an animal or man in a closed hot-air bath.

Characters of Sweat.—Pure sweat is neutral or alkaline in reaction; sometimes it is just acid. This is due to NaH_2PO_4 and fatty acids. In acute rheumatism sweating is profuse, and the reaction of the sweat is then acid. The peculiar odour of sweat is due to volatile fatty acids. The taste is salty; the specific gravity is about 1005.

Composition of Sweat:—

Water	98 to 99 per cent.
Solids	1 to 2 ,,
$NaCl$, Na_2HPO_4, KCl and Alkaline sulphates.	
Fatty acids.	
Urea (trace only) . .	0·08 per cent.

In diseases of the kidney, when little or no urine is excreted, the amount of urea in the sweat is increased. Sweat may contain squamous cells and also isocholesterin derived from the sebum.

Man is said to excrete about 2 lb. of sweat in twenty-four hours; some of this leaves the surface of the skin at once (insensible perspiration), some, on the other hand, remains for a time as drops of fluid (sensible perspiration). Occasionally sweating may be excessive (hyperidrosis), sometimes the sweat is foul-smelling (bromidrosis), sometimes it is tinged with colour, such as blue, green, or red (chromidrosis).

The Nervous Mechanism of Sweating.—

1. The Sweat Centres.—According to Adamkiewicz, the dominating centre is in the floor of the fourth ventricle. This centre is directly influenced by an altered condition of the blood which normally supplies it. The centre may be stimulated to increased activity by a distinct rise in the temperature of the blood; by CO_2, which accumulates in the blood in asphyxia; and by drugs (diaphoretics or sudorifics),

such as camphor, opium, pilocarpine, and alcohol. There are subsidiary sweat centres in the grey matter of the lower cervical and upper lumbar regions of the spinal cord.

2. The sweat centre in the medulla may be reflexly influenced by AFFERENT IMPULSES reaching it from without. Experimental stimulation of the upper cut end of the sciatic, or anterior crural nerves of an animal will cause reflex sweating. Stimulation of the mucous membrane of the mouth and stomach by hot substances, such as hot spiced drinks and food, will cause reflex sweating. Painful sensations often produce an increased activity of the sweat centre.

3. EFFERENT IMPULSES pass out of the spinal cord in the cervical region by the anterior nerve roots (sixth, seventh, and eighth cervical nerves); these medullated nerves pass into the nearest ganglion (stellate ganglion), which is their cell station. The sweat impulses pass along non-medullated nerve fibres, with the vasomotor nerves into the ulnar and median nerves, down the arm. Some of the impulses pass up the cervical sympathetic to the head and neck. Some efferent impulses, however, leave the sweat centre in the medulla, and pass through the three branches of the fifth cranial nerve to the forehead and face.

The efferent impulses for the leg leave the spinal cord by the last three dorsal and upper two or three lumbar nerve roots, and pass along medullated nerve fibres to the lateral ganglia, then by non-medullated nerve fibres with the vasomotor nerves to the sciatic. These sweat nerve fibres must end in the sweat glands, as they may be paralysed by belladonna and atropine (anhidrotics or anti-sudorifics), which diminish secretions and excretions generally by paralysing secreto-excitor nerve terminals. On the other hand, pilocarpine and physostigmine cause an active secretion of the sweat glands by stimulating the sweat nerve-endings.

FUNCTIONS OF THE SKIN.

1. **Protection.**—The skin acts as an organ of protection, covering in the more delicate structures. Moreover, where most protection is required there the skin is thickest. The skin is particularly thick on the palms and soles. On the dorsum the dermis is, as a rule, thicker than over the ventral aspect of the body.

2. **A Sense Organ.**—The skin is plentifully supplied with nerve endings, which are present in both the epidermis and dermis. In the epidermis there are the intra-epithelial plexuses of fine non-medullated nerve fibres. In the dermis are specialised organs called "corpuscles" in which medullated nerve fibres end. These corpuscles include the *Pacinian corpuscles*, which are placed upon the cutaneous nerves of the hands and feet. They are probably connected with pressure sensations. *Touch corpuscles of Meissner* occur in the bloodless papillæ of the dermis of the fingers and toes, and these are associated with pressure sense. The touch corpuscles of Meissner are more numerous where hairs are absent. Fine nerve plexuses are found around the hair follicles, just within the outer root sheath, beneath the entrance of the duct of the sebaceous gland, and these too are associated with pressure sense. *End-bulbs* occur in the dermis of the lips, and are probably connected with sensations of cold. The surface of the skin may be considered as consisting of minute areas, each of which subserves a specific sense, *e.g.* pressure sense, heat sense, cold sense, painful sense, and it is very probable that each area or spot coincides with a special sense corpuscle. The different varieties of sensation derived from the skin are due to the adequate stimulation of the specialised sensory end-organs present. This subject is dealt with in greater detail in the chapter on sensations.

3. **Respiration.**—*A very small amount* of carbon-dioxide leaves the body by the skin and the membrana tympani, so that in man this function is relatively unimportant. In frogs (hibernating animals) there is a special pulmo-cutaneous circulation by which venous blood is carried to the skin to be oxygenated, and the arterial blood so produced returned from the skin to be circulated.

4. **Heat Regulation.**—In this way the skin has a double action, for it helps in regulating heat production and heat loss.

Heat Production.—The temperature of the surrounding atmosphere, within certain limits, causes afferent impulses to start in the skin, and to travel by afferent nerves to the spinal cord; these impulses travel up to the thermogenic centre in the hind-brain; here efferent impulses arise which descend the cord, and, leaving by the anterior nerve roots, arrive at the muscles. The effect of these impulses is to *partly* regulate oxidation processes (katabolism) as they occur there. The effect of cold is to reflexly increase oxidation in the tissues by which more carbon-dioxide is produced in the tissues, and consequently more body heat evolved. On the other hand, the effect of a high external temperature is reflexly to partly inhibit oxidation processes in the tissues, so that less carbon-dioxide is evolved and consequently less heat produced.

HEAT LOSS.—Two mechanisms are involved in the process of the regulation of heat loss, namely, the vasomotor and the sweat. If it is necessary that there should be increased heat loss from the skin, *vaso-dilatation* occurs, so that more blood is brought to the surface, and heat is consequently lost by conduction and radiation. At the same time, there is an *increased excretion of sweat* (sensible prespiration), and heat is consequently lost by evaporation from the surface. The converse takes place when more of the body heat is retained by the organism.

If an animal with a delicate skin, such as a rabbit, is covered with an impermeable varnish, the animal soon dies of cold, its temperature being lowered. This is brought about by interference with the heat-regulating mechanism of the skin of the animal.

5. **Absorption.**—In an ordinary way absorption does not take place from unbroken skin, but slight absorption can be brought about by the cutaneous interepithelial spaces and the lymphatics of the dermis. If cod liver oil is rubbed into the abdominal wall, or placed on the binder, of a young child a small amount is undoubtedly absorbed. Mercurial ointment, if properly rubbed into the skin, is readily taken up by the lymphatics, and in this way mercury may be conveniently administered. When vaccination is performed the vaccine is introduced into the interepithelial spaces of the deeper layers of the epidermis by the removal of the superficial layers by an appropriate needle. It is readily taken up by the lymphatics, and produces the local and general signs and symptoms of vaccinia.

6. **Secretory Organ.**—Sebum is secreted by the cells lining the sebaceous glands, and acts as a natural lubricant for the hairs. Cerumen is secreted by the glands in the external auditory canal in order to lubricate the hairs and the membrana tympani.

7. **Excretory.**—Sweat may be looked upon as a secretion, but it is certainly one way by which water, inorganic salts, and traces of urea are eliminated from the body. In some cases of kidney disease, when the more important products of metabolism are no longer normally eliminated by the kidneys, sudorifics are administered, sweating is increased, and many of the waste products, such as urea, are in this way eliminated from the body. Occasionally, in disease of the kidneys, large quantities of urea are excreted in the sweat, and it is said that the amount excreted may be so large that the fine white crystals of urea may be readily detected on the surface of the skin (uridrosis).

SECTION X.

EXCRETION.

CHAPTER XXXIV.

THE KIDNEYS.

THE kidney is surrounded by a thin capsule of fibrous tissue which can be very readily pulled off. At the hilum of the kidney the capsule becomes continuous with the outer coat of the ureter. The kidney substance proper consists of two portions,—the outer, the cortex, and the inner, the medullary portion. The line of demarcation between these two is the presence of the arterial and venous arches. In the cortex are the capsules of Bowman, and the convoluted tubules with the interlobular arteries and veins. The medulla consists of two portions, the outer known as the boundary zone, and the innermost portion known as the papillary zone. The papillary zone consists of the bases and the apices of the kidney papillæ, of which there are usually from eight to twelve in the human kidney. Each papilla opens into a calyx or cup, and the calyces converge to form the pelvis of the kidney. In the medullary portion of the kidney are the collecting urinary tubules bound together by a small amount of connective tissue, and the ducts of Bellini together with the straight arteries and straight veins. These together form the medullary rays of Ferrin.

The kidney substance consists of three chief portions,—the urinary tubules, the blood vessels, and the intertubular connective tissue containing the lymph spaces.

Minute Structure of the Urinary Tubule.—The urinary tubule commences in a reflection of flattened epithelial cells around a tuft of capillaries; this reflection is known as

Bowman's capsule. The lining of Bowman's capsule consists of a flattened epithelium. The portion of the tube, continuous with Bowman's capsule, is called the *neck* of the tubule, and is lined on its inner aspect by one layer of flattened epithelial cells. In the frog the cells lining the neck of the tubule are ciliated. The tubule now widens out and becomes convoluted, the *first convoluted tubule.* The cells lining it are cuboidal and the protoplasm is striated, the striations being towards the basement membrane which supports the cells. The tube then becomes spirally arranged, the *spiral tubule*, and this is lined by cubical striated, or fibrillated cells. The tube then turns down towards the boundary zone, forming the *descending limb of the loop of Henle.* This tube is narrow, and lined by spheroidal cells. The tube then forms a **U**-shaped loop, the *loop of Henle*, where the spheroidal cells become replaced by cuboidal cells. The tubule then ascends from the boundary zone to the cortical part of the kidney, forming the *ascending limb of the loop of Henle.* It is broader than the descending limb, and lined by cubical striated cells, though the striations are not so definitely seen as in the cuboidal cells of the convoluted and spiral tubules. The ascending limb of the loop of Henle continues as the *irregular or zigzag tubule*, where the cells are again cuboidal and striated. The zigzag tubule is succeeded by the *second convoluted tubule*, which loops back in intimate relationship with the first convoluted tubule. The cells lining the second convoluted tubule are cuboidal and striated. The second convoluted tubule continues as the narrow *junctional tubule*; the cells lining it are cuboidal. The junctional tubules open into the *straight or collecting tubules* which are found in the cortex of the kidney. These collecting tubules descend through the medulla; the cells lining them are flattened columnar or cubical cells with no striations. The collecting tubules join with others to form one of the *ducts of Bellini.* These ducts, which are lined with columnar cells, traverse the papillæ, and open on to their apex, and in this way the urine reaches the pelvis of the kidney.

The Arrangement of Blood Vessels.—The renal arteries, which are branches of the abdominal aorta, break up in the kidney substance between the cortex and the boundary zone of the medulla, forming a number of incomplete arterial arches. From the convexity of these incomplete arterial arches are given off the interlobular arteries which traverse the cortex of the kidney. These interlobular arteries give off in a branch-like manner the afferent glomerular arterioles. These arterioles have plain muscle in their walls, and are probably supplied by vaso-motor nerves. The afferent glomerular arterioles end in the glomerular capillary plexuses, which are surrounded by Bowman's capsules. The glomerular capillaries converge to the efferent glomerular vessel, which contains in its walls plain muscle, and is probably also supplied by vasomotor nerves. The lumen of the efferent glomerular vessel is only two-thirds that of the afferent glomerular vessel. The efferent glomerular vessel breaks up into a secondary capillary plexus, and this plexus is situated around the convoluted tubules. The blood is collected from the secondary capillary plexuses by venules, which converge to form the interlobular veins which lie parallel with the interlobular arteries. The interlobular veins commence in the stellate veins, which are in the subcapsular layer of the cortex of the kidney, where there are no glomeruli. The interlobular veins open into complete venous arches, which lie alongside the incomplete arterial arches occurring between the cortex and the boundary zone of the medulla.

From the concavity of the incomplete arterial arches straight arterioles run through the boundary zone of the medulla. These are the true arteriæ rectæ, and break up into a number of straight capillaries, which are in intimate relationship with the descending limb of the loop of Henle, the loop itself, the ascending limb of the loop, and the collecting tubules. From some of the afferent glomerular arterioles near the boundary zone, small arterioles run back from the cortex into the boundary zone of the medulla, which are called the false arteriæ rectæ, and break up into straight capillaries. The blood is collected from the boundary zone and the papillary zone of the medulla by straight veins, which open into the concavity of the complete venous arches. The venous arches converge to form the renal veins, and the renal veins open into the inferior vena cava. In the intertubular connective tissue are the lymph spaces, which contain the tissue fluid or lymph. At the hilum of the kidney are the ureter, the renal artery with the vasomotor nerves, the renal vein, and the lymphatics.

The nerves to the kidney leave the spinal cord in the anterior roots of the eleventh, twelfth, and thirteenth thoracic nerves in the dog, and pass thence into the renal plexus. The local ganglia, namely, the cœliac, mesenteric, and renal, are cell stations for the fibres which are non-medullated (vaso-constrictor) and medullated (vaso-dilator). These fibres pass along the renal artery to the kidney.

The Functions of the Kidney.—

1. To excrete certain waste products and water.

2. To form hippuric acid. This change is brought about by an enzyme secreted by the renal cells. Benzoic acid and glycine are synthesised to form hippuric acid (*vide* p. 457).

3. To control the reaction of the urine, by producing acid sodium phosphate.

4. To preside over the composition of the blood plasma. If there is a rise in the percentage of its normal constituents they are excreted by the renal cells. As an example of this it may be noted that the percentage of dextrose in blood plasma varies from 0·12 to 0·2. If, however, the amount present is higher than 0·2 per cent. (a condition called hyperglycæmia), the renal cells excrete the excess, which appears in the urine (glycosuria). If abnormal constituents are present in the plasma, the kidney, as a rule, excretes these, *i.e.* if egg-albumin, albumose, or peptone is present in the blood plasma, it is excreted by the kidney. If poisons are present in the blood plasma, the kidney endeavours to excrete them. In diabetes mellitus β-hydroxybutyric acid occurs in the blood, and is excreted into the urine. In typhoid or enteric fever the typhoid bacilli are sometimes found in the urine. Drugs administered by the mouth may be detected in the urine. As examples the following may be mentioned: senna, logwood, santonin, potassium iodide, potassium bromide, etc. These are excreted by the urinary tubules.

THE EXCRETION OF URINE.

The excretion of urine depends upon three chief factors—

1. The capillary blood pressure in the glomeruli.
2. The velocity of blood flow through the renal vessels.
3. The physiological or biotic activity of the cells lining the urinary tubules.

1. **The Excretion of Urine depends upon the Capillary Blood Pressure in the Glomeruli.**—The pressure in the glomeruli is probably regulated by the afferent glomerular arterioles, which have plain muscle in their walls and are probably controlled by the vasomotor nerves. The kidney may be placed in an oncometer, and a catheter introduced into the ureter; the number of drops of urine passed in a given time may thus be counted. If the renal nerves which accompany the renal artery are divided, it is found that the kidney volume is increased; this is due to vaso-dilatation, the pressure of the blood in the renal glomeruli rises, and the urinary output is correspondingly increased. If the peripheral cut end of the divided renal nerves is stimulated by rapidly interrupted induced shocks, the kidney volume becomes diminished; this is due to vaso-constriction of the afferent glomerular arterioles and the efferent glomerular vessels. There is consequently a fall of the intracapillary pressure in the glomeruli and the secondary capillary plexuses, and the output of urine is diminished. If, however, the peripheral cut end of the renal nerves is stimulated rhythmically by slowly interrupted induced shocks, active vaso-dilatation of the renal arterioles occurs. There then follows an increase of intracapillary pressure, and the output of urine is increased.

It is found that if the aortic blood pressure falls below 40 mm. of Hg the excretion of urine stops. Drinking a large volume of fluid increases the output of urine. This is due to the fact that the fluid causes hydræmic plethora, which causes an increased volume of blood to circulate through the kidney; this induces the renal arterioles to dilate, producing an increase of intracapillary pressure.

Constriction of the cutaneous and other arterioles is, as a rule, associated with dilatation of the renal arterioles, and this causes a rise of intracapillary pressure and an increased output of urine. It has been found experimentally that if pituitary extract, derived from the nervous portion of the gland, is injected intravenously into an animal, there is vaso-dilatation of the renal arterioles and an increased output of urine.

2. **The Excretion of Urine depends upon the Velocity of Blood-Flow through the Glomeruli.**—That is to say, there must be a rapid removal of blood from the glomerular capillaries and secondary capillary plexuses in order that excretion may

take place. The velocity of the blood flow depends mainly upon the frequency and the force of the heart beat. If the frequency and the force of the heart beat are diminished by faradising the peripheral cut end of the vagus nerve, the excretion of urine becomes diminished. Digitalis causes an increased force of heart beat, and consequently diuresis. It has been found, however, that compression of the renal vein, causing a rise in the capillary blood pressure of the kidney, does not produce an increased output of urine. This is probably due to the fact that the engorgement of the renal capillaries causes an increase in extravascular tissue fluid (œdema), which presses upon the limbs of the loop of Henle, and therefore mechanically obstructs the urinary output; such compression, too, interferes with the velocity of the blood-flow. It is a well-known fact that, in valvular disease of the heart, with broken cardiac compensation, when the arteries of the body are underfilled and the veins overfilled, and consequently a rise of venous blood pressure, in which the kidneys participate, the output of urine is diminished. This is probably due to two causes, namely, (1) the mechanical obstruction of the urinary tubules, and (2) the low arterial blood pressure.

3. The excretion of urine depends upon the activity of the cells lining the urinary tubules. The exact part played by these cells is not definitely known, but the function of the cells which line the urinary tubules may be gathered from the following theories which have been advanced wtth regard to the excretion of urine.

THEORIES OF THE EXCRETION OF URINE.

A. Bowman's Theory.—This theory was built up mainly upon the general structure of the kidney, and upon the high blood pressure which exists in the renal arteries, and the low pressure in the renal veins. It supposes that the watery part of urine, together with the soluble inorganic salts, filters from the glomerular capillaries through the flattened epithelial cells of Bowman's capsule into the lumen of the tubule, *i.e.* filtration takes place at Bowman's capsule. The nitrogenous substances of urine, such as urea, creatinine, uric acid, etc. are excreted by the cubical striated cells which line the convoluted, the spiral, and the zigzag tubules, from the blood in the secondary capillary plexuses, and are passed into the lumen of the urinary tubules. Water passes through above, washes down and dissolves the solids which are excreted below.

HEIDENHAIN'S EXPERIMENT.—The results of this experiment, to a very considerable extent, support Bowman's view. The spinal cord of a rabbit is severed from the medulla, the result of which is to lower the arterial blood pressure. Ten c.c. of a saturated solution of sodium sulph-indigotate (a blue nitrogenous substance) are injected into the jugular vein of the animal, and artificial respiration is kept up for ten minutes. During this time the circulation goes on, and the sodium sulph-indigotate is distributed through the body. The artificial respiration is then stopped and the animal dies. The kidneys are rapidly removed and placed in alcohol, in order that they may become fixed and hardened. Sections are then cut in the usual manner and mounted *unstained*. Blue granules are found in the cubical striated cells lining the convoluted, the spiral, and the zigzag tubules, also in the cubical cells lining the ascending limb of the loop of Henle; blue granules are found in the lumen of the urinary tubules. There are no blue granules found in the epithelium lining Bowman's capsule, nor are there any blue granules found in the spheroidal cells lining the descending limb of the loop of Henle. The conclusions which are drawn from this experiment are, that the flattened cells lining Bowman's capsule excrete water and the inorganic salts of the urine, namely, sodium chloride, and possibly other soluble substances, such as sugar, when it is present in the urine, and that the cubical striated cells of the convoluted, the spiral, and the zigzag tubules, and the ascending limb of the loop of Henle, excrete the organic constituents of the urine, such as urea, creatinine, and uric acid.

Uric acid, which takes the place of urea in the urine of birds, has been traced through the cubical cells of the urinary tubules in much the same way as the blue granules of sodium sulph-indigotate.

NUSSBAUM'S EXPERIMENT.—Nussbaum performed his experiment upon large frogs. It should be remembered that the kidney of the frog receives a double blood supply. The renal arteries come from the aorta, and these supply the glomeruli and are partly distributed to the convoluted tubules.

Part of the femoral vein joins with the sciatic vein to form the renal portal vein, which runs up on the outside of the kidney, and breaks up, in the kidney substance, to form the secondary capillary plexuses. Nussbaum ligatured the renal arteries, consequently cutting off the blood supply to the glomeruli. He found, as a result, that the excretion of urine stopped. He then injected urea into the blood stream of the animal, with the result that the excretion of urine was re-established. This experiment suggested that the urea and some water were excreted from the secondary capillary plexus by the convoluted tubules, the urea having got round by the renal portal vein. He then injected into the blood stream of the frog, a solution of dextrose, and also in another experiment a solution of commercial peptone, and he found that these were not excreted in the urine. During these experiments it is necessary to keep the frog in an atmosphere of oxygen, which helps to maintain the functional activity of the renal cells. The conclusion drawn was that such substances as dextrose, albumose, and peptone, when they occur in the urine, are excreted through Bowman's capsule. It has been suggested that this experiment is somewhat fallacious,

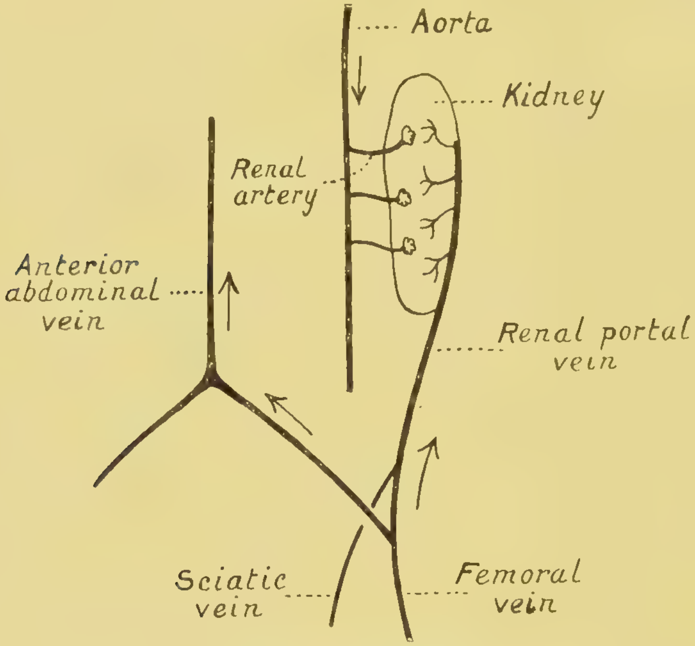


FIG. 53.—Diagram showing the double blood supply to the kidney of the frog.

because there is a direct communication between the glomeruli and the secondary capillary plexuses; moreover, there is a fairly free anastomosis between the renal arteries of the frog and the arteries of the testis or the ovary.

The experiment of Nussbaum has been recently repeated, in accord with recent knowledge. The thighs of the frog were ligatured to prevent the return of blood from this region to the kidneys. An oxygenated Ringer's solution was injected back through the anterior abdominal vein, and this reached the renal portal vein. No excretion of urine followed. Diuretics, such as urea or caffein, were then added to the oxygenated Ringer's solution, with the result that urine was excreted. Moreover, the flow of urine was accompanied by increased metabolism occurring in the renal cells, for more oxygen disappeared from the Ringer's solution when diuresis occurred than when no flow of urine was obtained.

B. LUDWIG'S THEORY.—Ludwig suggested that the fluid part of the blood plasma,—that is, the water and the salts (inorganic and organic) in solution, filters through from the glomerular vessels into Bowman's capsule, and that the function of the cubical cells, lining the convoluted tubes, is to reabsorb a large amount of the water, and to pass it through into the secondary capillary plexuses which are around the convoluted tubules, and at the same time to secrete back into the blood stream a certain amount of salt. That is to say, the function of Bowman's capsule is purely a physical one (filtration), and the function of the convoluted tubules is a physiological one, since re-absorption of much water and of some salt takes place here.

WORK DONE BY THE RENAL EPITHELIAL CELLS.

The osmotic pressure of a fluid varies directly with the amount of salt in solution. It is calculated that the osmotic pressure of the blood plasma is equivalent to a 0·92 per cent. solution of sodium chloride, and the osmotic pressure of the urine corresponds with a 4 per cent. solution of sodium chloride. That is to say, the osmotic pressure of the blood on one side of the renal epithelium is much less than the osmotic pressure of the fluid in the renal tubule on the opposite side of the epithelium. It is obvious, therefore, that the renal epithelial cells have to do a very considerable amount of work in excreting salt against a rising osmotic pressure, for the renal epithelial cells have to excrete salts until their osmotic pressure in the renal tubules corresponds with that of a 4 per cent. solution of sodium chloride. It is concluded, therefore, that the function of the flattened epithelial cells lining Bowman's capsule is to allow filtration to take place into the renal tubule, but at the same time that these cells have a definite excretory function, that is, they have a true physiological function to perform. The cubical striated cells, which line the convoluted tubes and the ascending limb of the loop of Henle, also excrete salts from the capillary blood stream into the urinary tubules.

The Conclusion to be Drawn.

As the result of these experiments, it may be concluded that the function of the epithelial cells lining Bowman's capsule is to allow of the filtration of water into the urinary tubule; at the same time that these cells excrete the inorganic salts of the urine, such as sodium chloride and the sulphates, and that, should the amount of dextrose in the blood stream rise beyond 0·2 per cent., these flattened cells excrete it into Bowman's capsule; and that abnormal constituents of the blood, such as albumose and peptone, are also excreted at Bowman's capsule. Further, that the function of the cubical striated cells in the urinary tubule is to excrete important organic constituents of the normal urine, such as urea, creatinine, uric acid, together with phosphates and nitrates; at the same time, these cells, if under the influence of phloridzin or phloretin, excrete dextrose from the blood stream into the urinary tubules. The spheroidal cells lining the descending limb of the loop of Henle, and the flattened cells lining the junctional tubule, and the simple cubical cells lining the collecting tubules, reabsorb a certain amount of water, and pass it back into the adjacent capillary blood stream.

THE VOLUME OF URINE.

The amount of urine excreted by the kidneys in twenty-four hours is between two and three pints, or about 1500 c.c. (50 oz.). This amount, however, varies considerably. It may be increased in the following circumstances:—

1. With an increased intake of fluids, which produce

hydræmic plethora. This causes a slight rise of blood pressure, and a definite increase in the capillary blood pressure of the kidney.

2. With an increase in arterial blood pressure due to an increased force of heart beat, such as occurs when digitalis is administered.

3. Constriction of the cutaneous arterioles, as occurs in cold weather. In these circumstances the arterioles of the splanchnic area dilate; this includes the vessels of the kidney. There is consequently a rise in the capillary pressure in the glomeruli, and diuresis follows.

4. Under the influence of diuretics. How these act has not been definitely determined, but it is possible that they may act in one, or all, of the following ways:—

(*a*) Saline diuretics cause a rise in the osmotic pressure of the blood plasma; the result of this is that water is attracted from the tissues, and hydræmic plethora follows. There is consequently a slight rise of arterial blood pressure, with a general dilatation of the visceral arterioles. This causes a rise of the capillary and venous pressure, and therefore an increased rapidity of blood flow.

It is found that the vaso-dilatation in the visceral area is more marked in the kidney. There is therefore, in the kidney, a relatively greater rise of capillary pressure, and consequently a greater tendency for filtration at the glomeruli to take place into the urinary tubules.

(*b*) It is very possible that the salts in solution in the blood plasma have a direct action upon the renal epithelial cells. It has been found that, after the injection of sodium sulphate and of sodium chloride, the vascular changes in the kidney are of the same kind, and occur in the same degree; but it has also been found that there is more diuresis after the injection of sodium sulphate than after the injection of sodium chloride, which suggests a specific action of the various saline diuretics, and that these salts probably act directly upon the flattened epithelium lining Bowman's capsule. It has been already stated that caffeine probably acts by stimulating the cubical cells lining the convoluted tubules.

In support of the theory that diuretics directly stimulate the cells lining the urinary tubules to increased activity, is the fact that diuresis is accompanied by an increase of oxygen used by the kidney, indicating increased metabolism.

5. Nervous influences have an effect upon urinary excretion. As an example, diuresis occurs under emotional conditions, such as the excitement associated with an examination. Nervous phenomena also explain the polyuria of diabetes insipidus.

6. The output of urine is increased when the renal epithelial cells are irritated. This occurs when the amount of dextrose in the blood plasma is greater than 0·2 per cent., and in part explains the polyuria accompanying the glycosuria which occurs in diabetes mellitus.

The output of urine may be decreased under the following conditions :—

1. When more fluid is lost by the skin,—*e.g.* after profuse sweating.

2. When much fluid is lost by the bowel, as is the case during an attack of diarrhœa.

3. When there is a diminished intake of fluid.

4. When there is a low arterial blood pressure. It has been already stated that when the aortic blood pressure falls below 40 mm. Hg. the excretion of urine stops. In "shock" the urine becomes scanty, from the general fall of arterial blood pressure.

5. Lastly, when there is a passive congestion of the renal veins, as may be brought about by local compression, the excretion of urine becomes diminished; this is due to the resulting œdema of the intertubular connective tissue interfering with the passage of fluid along the convoluted tubules.

Effect of Removal of the Kidneys.—If one kidney is removed the other hypertrophies and does the work of two. If both kidneys are removed, urea and other waste products of metabolism are retained in the body, and death follows from auto-intoxication. Such a result occasionally occurs in man when one kidney is absent, or is not functioning on account of disease, and the ureter of the other kidney becomes completely blocked by a renal calculus. If the obstruction is not removed, the individual suffers from anuria, or suppression of urine, and dies of auto-intoxication. There are usually no convulsions.

If both renal arteries are ligatured, the kidneys become asphyxiated, and urine is not excreted. If the ligatures are cut, urine is again excreted after a short time, but it contains serum globulin and serum albumin. These proteins escape from the blood; this is due to the changes in the cells of the urinary tubules brought about by the cutting off of their blood supply.

Phloridzin and the Kidneys.—If phloridzin, or phloretin, is injected into the blood of an animal, sugar, probably derived from tissue proteins, appears in the urine. If the phloridzin is injected into a renal artery, sugar appears in the urine from that kidney before it appears in the urine from the opposite kidney. The sugar which is present in the urine is most probably *excreted* by the cubical striated cells lining the convoluted tubules. If the kidney is diseased the excretion of sugar, due to the administration of phloridzin, is less than from a normal kidney. The excretion of sugar may even be absent from a diseased kidney.

This test has been used in demonstrating the glandular activity of the kidney in cases of suspected renal inefficiency. A catheter is introduced into each ureter, phloridzin administered to the patient, and the urine, flowing from each catheter, examined for sugar.

The Passage of Urine along the Ureters.—The ureter consists of a muscular tube furnished with a lining of mucous membrane. The mucous membrane, like the bladder, is lined by a layer of transitional epithelium. The muscular coat is double, consisting of plain muscle fibres arranged in a longitudinal direction in the inner layer, and circularly in the outer. It is supplied with nerves of the sympathetic (autonomic) system derived from the mesenteric, spermatic, and hypogastric plexuses. In its coats are a few nerve cells, but these, Engelmann maintains, are absent from the middle third, although this has been denied by others. The entry of the ureter into the bladder is oblique, the two tubes converging towards one another, and each lies for as much as a half to three-quarters of an inch within the bladder wall before opening into the bladder. As soon as the tube has passed into the wall its circular fibres are combined into a kind of sphincter round the vesical orifice; the longitudinal fibres continue on through the wall to impinge upon the mucous membrane of the bladder, where they form a small papilla upon the top of which is the ureteral orifice.

The passage of the urine along these tubes depends upon two factors,—the pressure at which it is excreted into the urinary tubules, associated also, in the erect posture, with the hydrostatic effect of gravity and the peristaltic movements of the ureters. As a result of these factors, it is obvious that the urine will be emptied into the bladder in a discontinuous manner, each ejection corresponding in time with a peristaltic movement of the tube. This has been confirmed by actual observation. In cases of ectopia vesicæ (defect of the anterior wall of the bladder and the lower part of the anterior abdominal wall), in which the posterior wall of the bladder is exposed, the actual flow of urine from the vesical orifices of the ureters has been watched. It has been noted that the flow of urine is intermittent from each tube, and that no exact time relations exist between the flow of the two sides. The flow of urine is increased by raising the intra-abdominal pressure, as is done by straining, or by the performance of deep inspirations.

Peristaltic Movements of the Ureters.—These movements commence at the kidney end of the ureter, and progress downwards towards the vesical orifice at a rate of 20 to 30 mm. per second, and they succeed one another at time intervals of ten to twenty seconds. Like the intestinal movements, they may be initiated by artificial stimulation. A pinch of the tube produces a peristaltic movement down the tube, and also an abnormal anti-peristaltic movement passing up towards the kidney. These movements obviously stand in close relationship to the so-called rhythmic movements of the intestine. Such movements are myogenic in origin, and similarly the ureteric peristalsis is believed to be of muscular origin too. In fact, if Engelmann's view is correct, that no nerve cells exist in the middle third of the ureter, the myogenic hypothesis is incontrovertible. The movements appear also to be independent of the amount of fluid in the tube, and are confined absolutely to the ureter; they do not spread to the bladder.

Neuro-muscular Mechanism of the Bladder.—The plain musculature of the bladder is disposed in three coats,—"an outer principally longitudinal, a middle chiefly transverse, and an inner plexiform, but tending towards the vertical direction." At the same time, the inner layer is ill developed, and the distinction into the three layers is by no means obvious. The term detrusor urinæ is often applied to the musculature thus described. At the cervix of the bladder, where it is continued into the urethra, the circular layer is thickened to form a sphincter, often called the sphincter vesicæ internus. The nerves of the bladder form ganglionated plexuses.

The Urethra is surrounded by two coats of unstriped muscle—an inner longitudinal, and a thicker outer circular, continuations respectively of the inner and middle coats of the bladder. In addition, it is supported at certain intervals by other collections of striated and unstriated muscle tissue. Thus, in the female, certain striated muscle fibres belonging to the group of constrictors of the vestibule also surround and close upon the urethra. In the male, the constrictor urethræ membranaceæ and the accelerator urinæ belong to this category; as also does the external sphincter vesicæ, a striated muscle described by Henle, transversely directed and lying on the anterior face of the prostate gland.

Phenomena of Micturition.—In the empty condition the wall of the bladder is firmly contracted (systolic contraction), whilst the cavity is quite obliterated. The intravesical pressure is zero. The constrictor vesicæ is in a condition of tonic contraction, and consequently, when the urine arrives in the bladder, it is not immediately evacuated. The urine is retained and accumulates, being prevented from regurgitation through the ureters by the oblique course of these tubes through the coats of the bladder. Room is made for it by the gradual relaxation (not stretching) of the bladder walls. As the amount of urine increases, the bladder wall responds to the increased tension by a series of rhythmic contractions. These contractions increase in extent with increase of the intravesical tension. At the same time a desire to micturate is aroused. If micturition is performed, the voluntary muscles at the neck of the bladder are inhibited, the movements of the bladder are intensified (for the bladder muscle does to some extent respond to the will), and the abdominal muscles contract with the diaphragm fixed in the position of inspiration. As a result of this, the tension in the bladder is raised to such a height that it is greater than the resistance offered by the involuntary sphincters at the cervix. A few drops of urine are forced past the internal sphincter into the first part of the urethra. Here sensory nerve endings are excited, and reflexly, through the lumbo-sacral cord, the tonicity of the internal sphincter is inhibited, with the result that the urine escapes. The last drops of urine are expelled by the contractions of the lævatores ani and the accelerator urinæ (bulbo-cavernosus) muscles. Unlike the stomach in vomiting, it appears that it is the contraction of the detrusor urinæ, and not that of the abdominal muscles, which furnishes the force necessary for the performance of micturition. Should micturition not be performed, the bladder movements, after increasing in intensity for a short time, begin to diminish and finally cease. Similarly, the desire to micturate disappears. Micturition itself can be checked at any stage of its progress by voluntary contraction of the striated sphincter of the bladder.

It is evident that micturition is to be considered as a reflex act innervated through the lumbo-sacral cord, and involving two processes — strong contraction of the detrusor urinæ, accompanied by relaxation of the sphincters (especially the internal) at the neck of the bladder; moreover, the reflex does not necessarily involve consciousness. Goltz demonstrated the truth of this by showing that even in dogs, with the spinal cord transected in the lower dorsal region, micturition took place normally after recovery of the operation, especially on stimulation of the perineal region.

Nerves involved in Micturition.—The bladder is supplied by autonomic nerves from two sources, which reach it by way of the hypogastric plexus. The two sources are the sacral nerves and the inferior mesenteric ganglia. From the second, third, and fourth sacral-nerves small medullated nerve fibres are given off, which, via the pelvic splanchnics (Gaskell) or the nervi erigentes, pass immediately to the hypogastric plexus, missing the sympathetic chain of ganglia. Stimulation of these fibres causes a very strong contraction of the bladder. The other series of fibres arises in the third, fourth, and fifth lumbar nerves. They pass to the inferior mesenteric ganglion, in which lie the synapses between the pre-ganglionic and post-ganglionic neurones. The fibres of the post-ganglionic neurones pass by the non-medullated hypogastric nerves to the hypogastric plexus. Stimulation of these nerves, at any part of their course, produces a feeble action of the bladder.

As is well known, in the adult the micturition-reflex is under voluntary control, although in the young the reflex partakes more of an involuntary character.

The centres for micturition are in the grey matter of the lumbar region of the spinal cord. The centre which presides over the evacuation of the bladder, *detrusor centre* (detrusor contracted, sphincters inhibited) is situated rather higher than the centre controlling the bladder during the period of its filling, *i.e.* the *sphincter centre.* If a transverse lesion occurs in the spinal cord in the dorsal or lower cervical region, *i.e.* below the fourth cervical segment, control over the bladder is lost; and when it is full, *i.e.* when the intravesical pressure is high enough, the bladder empties itself reflexly. If, however, a lesion occurs in the lumbar region of the cord involving the detrusor centre, the detrusor muscle is paralysed, the sphincter remains contracted, the result of which is, the individual gets retention of urine. Later, when the distended bladder can hold no more urine, the urine slowly trickles away, a condition called "retention of urine with overflow" (false incontinence). If the sphincter centre is involved the muscle becomes paralysed and the detrusor contracts, the result of which is that, as the urine enters the contracted bladder, it escapes, a condition known as true or paralytic incontinence.

CHAPTER XXXV

THE URINE

Colour.—This is usually light yellow, due chiefly to the pigment *urochrome* which is largely present. Urochrome contains S and N, and it is probably derived from protein. It gives no absorption bands in the spectrum. Freshly passed urine contains a colourless chromogen, called urobilinogen, which, on exposure to the atmosphere, becomes oxidised to *urobilin*, a reddish pigment.

Hæmoglobin gives rise to bilirubin and biliverdin, which are present in the bile. These iron-free compounds are in the intestine converted into stercobilin, most of which leaves the body in the fæces; some, however, is absorbed from the intestine, and is excreted in the urine as urobilinogen. Urobilin gives one broad absorption band over the F line of the spectrum.

If concentrated urine is allowed to cool, urates are precipitated, which are usually dark pink in colour; this is due to the pigment *uroerythrin*. Uroerythrin gives two ill defined absorption bands,—one over the E and one over the F lines. If urine, to which a little strong hydrochloric acid has been added, is allowed to stand exposed to the atmosphere, it turns deep red; this is due to the formation of a pigment called *urorosein*. Urorosein gives one absorption band between the D and E lines of the spectrum.

Pigments abnormal to the urine may be present, such as bilirubin and biliverdin. Blood pigment may be present, when the colour varies from smoky to bright red. If blood corpuscles are present the condition is known as hæmaturia; if oxyhæmoglobin, or methæmoglobin is present in solution, the condition is known as hæmoglobinuria. Occasionally, in cases of poisoning by sulphonal, alkaline hæmatoporphyrin is present in the urine (hæmatoporphyrinuria). Drugs taken internally, such as rhubarb, santonin, hæmatoxylin, may

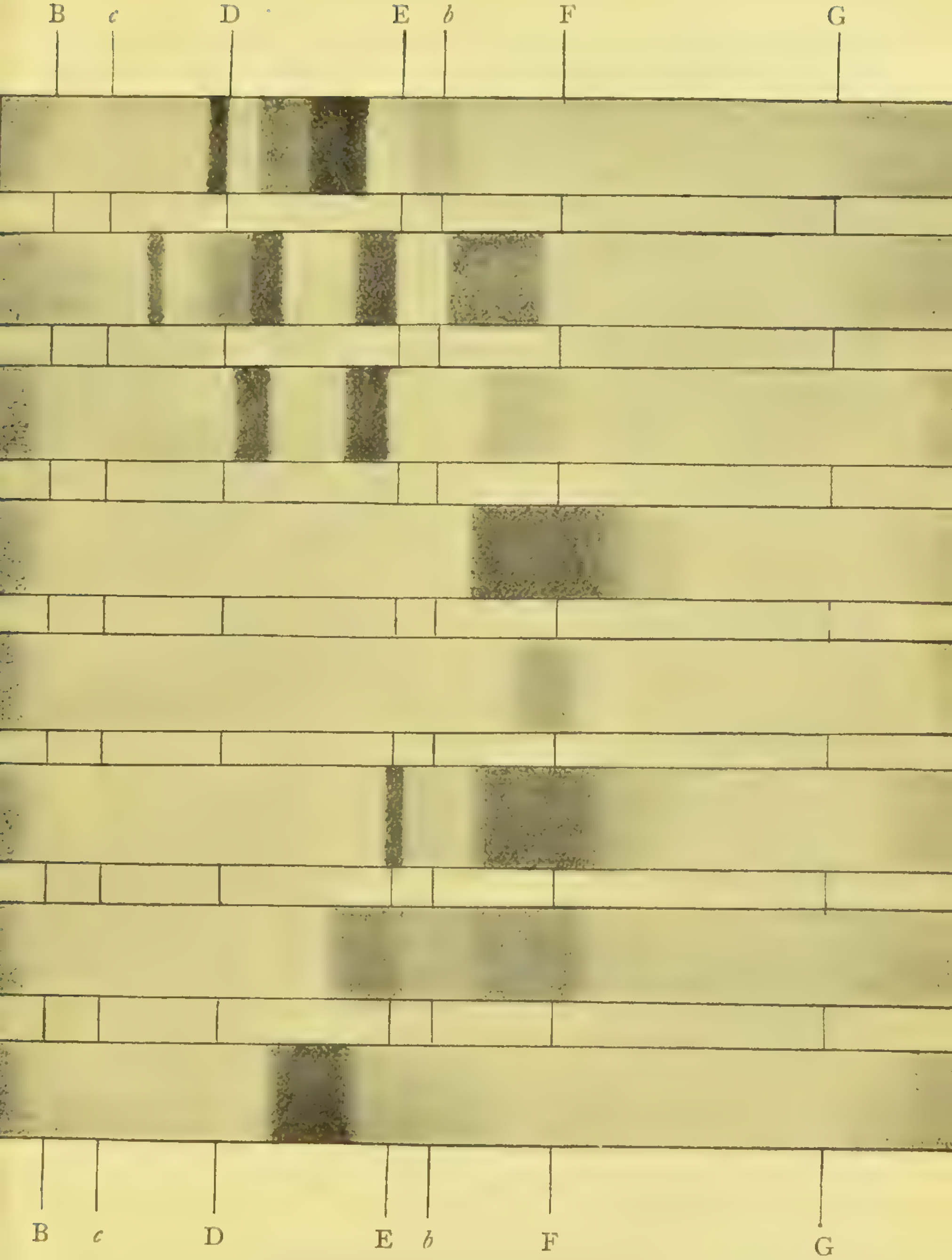


FIG. 54.—Chart of absorption spectra. (*After* F. Gowland Hopkins.)

1 = Acid hæmatoporphyrin.
2 = Alkaline hæmatoporphyrin.
3 = Hæmatoporphyrin as found in urate sediments.
4 = Acid urobilin (concentrated).
5 = Acid urobilin (dilute).
6 = The E band spectrum of urobilin.
7 = Uroerythrin.
8 = Uroroscin (concentrated), on dilution the absorption band shrinks rapidly from the redward end of the spectrum.

colour the urine. As a result of carbolic acid poisoning, the urine, especially on exposure to the atmosphere, becomes olive green (carboluria); this is due to the production of hydrochinone.

Reaction.—Normal urine is acid, due to acid salts, the most important of which is acid sodium phosphate (NaH_2PO_4).

The reaction of the urine varies—

1. *With the kind of food taken.*—Fruits and vegetables contain organic acids, such as citric, malic, and tartaric. These acids in the blood plasma are oxidised to *alkaline carbonates*, which are excreted in the urine. For this reason vegetarians often pass a neutral or even an alkaline urine.

2. *With digestion.*—During active digestion, when free HCl is being produced in the stomach, bases are liberated in the blood; and these, being excreted in the urine, diminish its acidity, or may even make it alkaline (*alkaline tide*). During fasting the urine becomes more acid (*acid tide*). The urine passed first in the morning is usually more acid than that which is passed later in the day.

3. *Decomposition.*—If urine is allowed to stand, and in cases of chronic cystitis (inflammation of the bladder), it frequently becomes alkaline with an ammoniacal smell. This is due to the decomposition of urea into ammonium carbonate

$$CO(NH_2)_2 + 2H_2O = (NH_4)_2CO_3 = 2NH_3 + H_2O + CO_2$$

The alkalinity of the urine which occurs in cases of chronic cystitis may be overcome by the administration of acid sodium phosphate or benzoic acid. The benzoic acid so given combines with glycine to form hippuric acid; this synthesis is brought about by the action of the renal cells.

Specific Gravity.—This varies between 1015 to 1025. If the specific gravity is below 1010 it may be due to copious drinking (urina potus), or to one of the causes of polyuria. If the specific gravity is higher than 1030, say 1035, it may be due to profuse sweating or copious diarrhœa. On the other hand, it may be due to an increased amount of solid in the urine, as occurs in diabetes mellitus.

The percentage of solids present in the urine may be determined from the specific gravity by multiplying the last two figures of the specific gravity by 2·2 and then moving the decimal point one place to the left. For example, if the specific gravity is 1018, the 18 is to be multiplied by 2·2, this gives 39·6, the decimal point is to be moved one point to the left, giving the number 3·96,—that is, if the specific gravity is 1018, the urine contains 3·96 per cent. of solid.

COMPOSITION OF NORMAL URINE

Water . . .	96 per cent.
Solids . . .	4 per cent., half of this is urea.

Organic solids—	*Amount excreted in twenty-four hours.*
Urea (2 per cent.) . . .	33 grms., or 500 grs.
Creatinine	0·9 ,, 15 ,,
Urates	0·75 ,, 10 ,,
Hippurates	0·4 ,, 6 ,,
Calcium oxalate (small quantities only).	
Ethereal sulphates.	

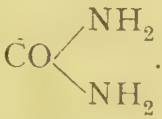
Inorganic solids—		
Sodium chloride . . .		10 grms., or 150 grs.
Chlorides Sulphates	of the alkalies Na.K.NH_4 and	1·5 to 3 grms., or 25 to 45 grs.
Phosphates	of the alkaline earths Ca.Mg	2·5 to 3·5 grms., or 40 to 50 grs.
Carbonates of Na, NH_4, Ca, and Mg may occur in alkaline urine.		

Colouring matter—

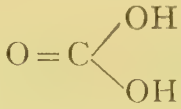
Urochrome.
Urobilin (urobilinogen).
Uroerythrin (traces).
Urorosein (traces on oxidation).

One hundred volumes of urine contain 15 volumes of gas; most of this is CO_2, there is a small amount of free N.

Urea, or Carbamide.

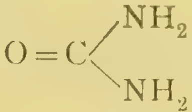
The formula for urea is  $\mathrm{CO}<^{\mathrm{NH_2}}_{\mathrm{NH_2}}$. It is isomeric with—

that is, has the same empirical formula as—ammonium cyanate $(NH_4)CNO$. Urea is the diamide of carbonic acid; that is, it is carbonic acid in which the two hydroxyl groups (OH) have been replaced by (NH_2) or amino groups.



$$O=C\begin{cases}OH\\OH\end{cases}$$

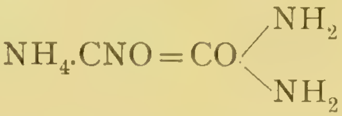
(Carbonic acid)



$$O=C\begin{cases}NH_2\\NH_2\end{cases}$$

(Urea)

Urea was the first organic body to be synthesised. In 1828, Wöhler first prepared urea from ammonium cyanate ; the atoms become rearranged thus :—

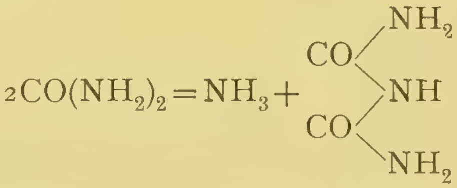


$$NH_4.CNO=CO\begin{cases}NH_2\\NH_2\end{cases}$$

Characters of Pure Urea.—It forms elongated colourless crystals, which have a salty taste. It is soluble in water and in alcohol, but insoluble in ether and in chloroform. It is neutral to litmus, although chemically it is basic, as it combines with acids to form salts, such as urea nitrate and urea oxalate.

TESTS FOR UREA.

1. Urea crystals, heated in a dry test tube, melt at 130° C. At 150° C. they are decomposed, NH_3 comes off and biuret remains, which gives a characteristic reaction. If a trace of $CuSO_4$ solution is added, and an excess of 20 per cent. KOH, a rose-red colour is produced. If the urea is heated to 170° C. cyanuric acid is produced ; this does not give the biuret coloration.



$$2CO(NH_2)_2=NH_3+\begin{matrix}CO\begin{cases}NH_2\\ \end{cases}\\ \quad\;\rangle NH\\ CO\begin{cases} \\NH_2\end{cases}\end{matrix}$$

(Biuret)

$$3CO(NH_2)_2=3NH_3+C_3N_3H_3O_3$$

(Cyanuric acid)

2. If urine is concentrated by evaporation, and concentrated HNO_3 added, characteristic octahedral crystals of urea nitrate [$CO(NH_2)_2.HNO_3$] are formed ; if oxalic acid is added, the more definite prismatic crystals of urea oxalate [$CO(NH_2)_2.(COOH)_2.H_2O$] are produced.

3. If to urine, fuming nitric acid (nitric with nitrous acid) is added, bubbles of CO_2 and N_2 are evolved, thus:—

$$CO(NH_2)_2 + 2HNO_2 = CO_2 + 2N_2 + 3H_2O$$

4. If to urine an *alkaline* solution of sodium hypobromite is added, nitrogen is liberated.

$$CO(NH_2)_2 + 3NaBrO + 2NaOH = 3NaBr + Na_2CO_3 + 3H_2O + N_2$$

This method is used for estimating urea quantitatively.

QUANTITATIVE ESTIMATION OF UREA BY DUPRÈ'S APPARATUS.

Into a special bottle are put 25 c.c. of an alkaline solution of sodium hypobromite, and lowered into this is a small vessel containing 5 c.c. of urine. The bottle, which is connected with a rubber tube to an inverted burette in a long vessel of water, is now tightly corked. Care must be taken that the apparatus is airtight. The 5 c.c. of urine are upset into the excess of the sodium hypobromite solution, nitrogen is evolved; this is carefully measured. The amount of urea present in the 5 c.c. of urine is calculated from the fact that 35·4 c.c. of nitrogen are yielded by 0·1 grm. urea.

PREPARATION OF UREA FROM URINE.

The urine is evaporated to one-sixth of its bulk in order to concentrate it. Concentrated HNO_3 is now added; if the mixture is kept cool, crystals of urea nitrate separate out.

The crystals of urea nitrate are collected, dissolved in alcohol, and barium carbonate added; the mixture is rubbed to a paste. The result is that CO_2 is given off, and barium nitrate and urea formed.

The urea is extracted with alcohol, which is then evaporated. Impure crystals of urea form. These crystals may be dissolved in water, animal charcoal added, and a black paste formed; the charcoal takes up the pigment from the urea, the urea may be again dissolved out and recrystalised.

Creatinine.

The composition of creatinine is $C_4H_7N_3O$. About 15 grains are excreted in twenty-four hours; the amount remains remarkably constant, diet and exercise having no apparent effect upon it.

TESTS FOR CREATININE.

1. *Jaffé's Test.*—To the urine a few drops of a saturated solution of picric acid are added, and a few drops of KOH, 20 per cent. solution; a deep red colour is produced.

2. *Weyl's Test.*—To the urine a few drops of a freshly prepared solution of sodium nitro-prusside and KOH, 20 per cent. solution, are added. A red colour is produced, which, however, fades on boiling.

Creatinine is usually estimated by the colorimetric method of Folin, which depends upon the red colour produced, as in Jaffé's test. This colour is compared with the colour of a standard solution of bichromate of potash.

Urates.

Two classes of urates may exist in urine, and their relationship to uric acid is as follows:—

$C_5H_4N_4O_3$, uric acid.
$C_5H_3NaN_4O_3$, acid sodium urate (the more abundant).
$C_5H_2Na_2N_4O_3$, normal sodium urate.

The pink precipitate, which occurs in concentrated urine on cooling, consists chiefly of acid sodium urate. Uric acid is sometimes combined with ammonia, forming acid ammonium urate. The chief characteristics of the precipitate of urates (lateritious deposit) are as follows: The urates are usually amorphous, precipitated in acid urine of high specific gravity; they are soluble on being heated, or on an alkali being added. Their pink colour is due to the pigment uroerythrin.

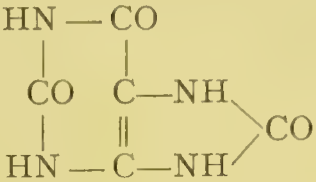
Uric Acid.

Uric acid is a diabasic acid, and is almost insoluble, requiring 1900 parts of hot water and 15,000 parts of cold water to dissolve one part of it. It is soluble in alkaline phosphates. Thus:—

$$Na_2HPO_4 + C_5H_4N_4O_3 = NaH_2PO_4 + \underset{\text{(Soluble acid sodium urate)}}{C_5H_3NaN_4O_3}$$

Uric acid is trioxypurine, and has the formula

$C_5H_4N_4O_3$, or



Uric acid crystals may be prepared from urine by adding to 100 c.c. urine, 5 c.c. strong HCl, and leaving it to stand in a cool place for twenty-four hours. The urine becomes dark in colour, due to the formation of the pigment urorosein, and dark uric acid crystals are precipitated. These may be collected, dried, dissolved in an alkali, and reprecipitated by adding HCl. Pure uric acid crystals are variously shaped: whetstones, rosettes, lozenge-shaped, barrel-shaped, and even dumb-bells. The weight of uric acid excreted bears a fairly constant ratio to the weight of urea eliminated in the urine; the average ratio is uric acid 1 to urea 50 (von Noorden).

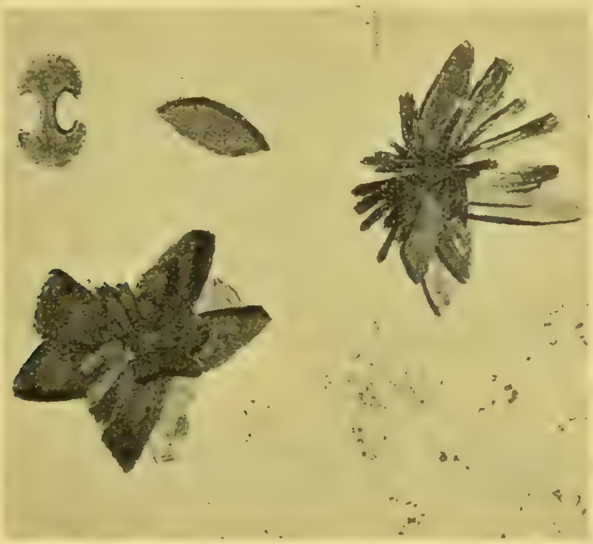


FIG. 55.—Uric acid crystals. In the lower half of the figure the crystals are shown as they separate when a quadriurate deposit is decomposed with water. (F. Gowland Hopkins.)

TESTS FOR URIC ACID.

Murexide Test.—Uric acid, or a urate, is placed in a capsule and a little dilute nitric acid added. The whole is evaporated to dryness, when a dirty yellow residue is left. If a little ammonia is added the colour becomes reddish purple, due to the formation of ammonium purpurate or murexide; if a little caustic potash solution is added, the colour becomes blue. The reaction depends upon the formation of alloxantin ($C_8H_4N_4O_7$), which with the NH_3 forms the purpurate of ammonia.

Schiff's Test.—Uric acid is dissolved in a solution of sodium carbonate. A drop of this solution is put on filter paper, and a drop of silver nitrate solution added. On being gently warmed the spot becomes darkened, due to the reduction of the silver.

ESTIMATION OF URIC ACID BY FOLIN'S MODIFICATION OF HOPKINS' METHOD.

To 100 c.c. urine add 30 grms. of ammonium sulphate, shake and make alkaline with ammonia; ammonium urate is precipitated; this should be filtered off.

The precipitated ammonium urate is then washed free from chloride with a 10 per cent. solution of ammonium sulphate.

The precipitate of ammonium urate is washed into a flask with hot water, and the solution allowed to cool.

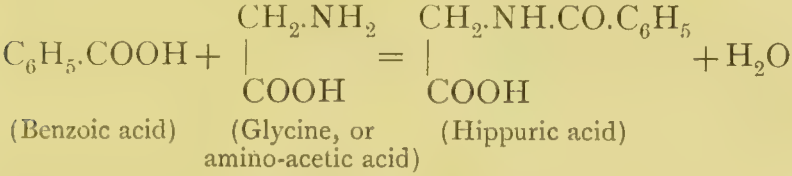
To the solution of ammonium urate 15 c.c. of H_2SO_4 (concentrated) are added.

The solution is then titrated with a solution of potassium permanganate (1·581 grms. to a litre of water), until a permanent rose colour remains. The temperature of the titrated fluid should be 60° C.

The number of c.c. of potassium permanganate used should be read off and multiplied by 3·75; this will give the quantity of uric acid in milligrammes contained in the 100 c.c. of urine originally taken.

Hippurates.

These are present in very small quantities in human urine, but in much larger quantities in the urine of the horse. Hippuric acid ($C_9H_9NO_3$) is formed by the cells lining the urinary tubules. Here, probably as the result of enzyme action, the benzoic acid of the food is synthesised with glycine produced from protein, or by the renal cells themselves to form hippuric acid, thus—



$$C_6H_5.COOH + \begin{array}{l} CH_2.NH_2 \\ | \\ COOH \end{array} = \begin{array}{l} CH_2.NH.CO.C_6H_5 \\ | \\ COOH \end{array} + H_2O$$

(Benzoic acid) (Glycine, or amino-acetic acid) (Hippuric acid)

If a mixture of benzoic acid, glycine, and defibrinated blood is injected into the renal artery, or mixed with the minced kidney cells just removed from the body and kept at body temperature, hippuric acid is formed. From 2 to 10 grs. of hippuric acid are excreted daily, but this amount depends upon the kind of diet.

Hippuric acid may be obtained as follows: Horse's urine is evaporated in order to concentrate it. Concentrated HCl is added, crystals of hippuric acid are deposited; these may be dissolved in boiling water, filtered, and recrystallised on cooling. The crystals so obtained form four-sided prisms in rosettes; they are soluble in hot water. These crystals may be dissolved in KOH or NH_3, and reprecipitated with HCl.

TEST FOR HIPPURIC ACID.

If the crystals of hippuric acid are heated in a dry test tube they melt at 186° C.; further heating causes the solution to turn red, a white sublimate of benzoic acid occurs, and an odour of bitter almonds is produced. This is due to the formation of phenyl-cyanide and hydrocyanic acid.

Calcium Oxalate.

This is sometimes precipitated, as envelope-shaped or less commonly dumb-bell crystals, in an acid urine (*vide* Fig. 56). Calcium oxalate crystals are soluble with difficulty in hydrochloric acid, but are insoluble in acetic acid and in ammonia. There are two chief sources of oxalates in the urine:

1. The ingestion of oxalates in the food, such as rhubarb, spinach, tomatoes, and strawberries.

2. Fermentation of sugar in the stomach, giving rise to oxalic acid; such fermentation occurs in the absence of HCl.

Excess of oxalates may cause the formation of urinary calculi of calcium oxalate.

Ammonia in Urine.

Ammonia is produced in the body as the result of protein katabolism, and most of it is converted into urea. Some, however, is used to neutralise the acids which circulate in the blood, and so the body is protected against "acidification." The excess of ammonium salts so produced appears in the urine, so that, to a certain extent, the amount of ammonia in the urine is an index of the amount of acid in the circulation.

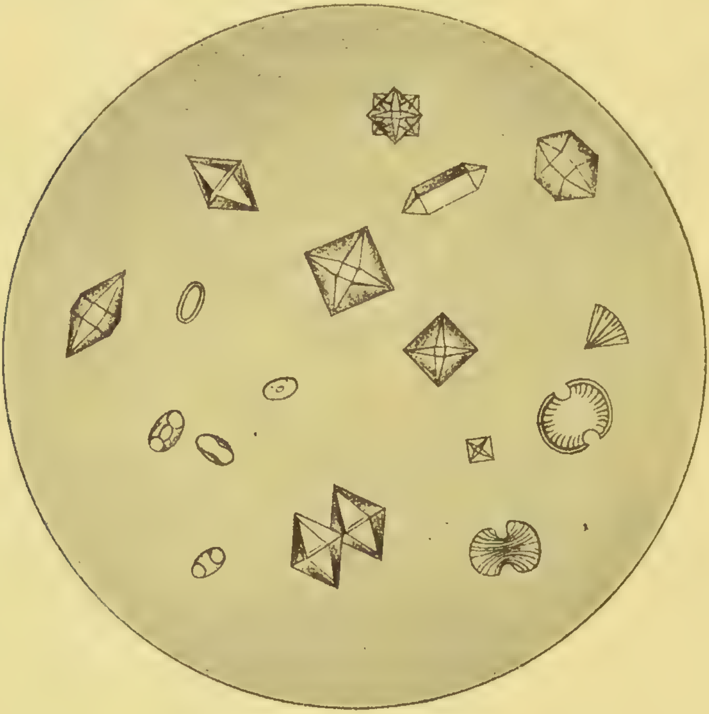


FIG. 56.—Calcium oxalate crystals. (Gibson and Russell.)

On an animal diet, in the later stages of diabetes mellitus, and also in some of the toxæmias associated with pregnancy, organic acids enter the circulation in large quantities, more ammonia is produced in the body, and consequently more is eliminated in the urine. On the other hand, on a vegetable diet, excess of alkali, either in the food or given as such, the ammonia may disappear from the urine, all the ammonia produced in the body being converted into urea.

The arterial blood (blood from the carotid artery contains 2 to 3 milligrms. of NH_3 per cent.) to the kidney contains a small amount of ammonium carbonate, the bulk of which will eventually get round to the liver and be converted into urea; a small amount does, however, escape into the urine. In man the average daily output of ammonia is 0·7 grm.

ESTIMATION OF THE TOTAL NITROGEN IN URINE.

This is carried out by Kjeldahl's method, which is briefly as follows:—

Into a Jena flask of 250 c.c. capacity are placed 10 c.c. of urine and 20 c.c. of pure H_2SO_4.

Potassium sulphate (6 grms.) and copper sulphate ($\frac{1}{2}$ grm.) are added, and the whole slowly heated to boiling-point, and the boiling continued for an hour. All the nitrogen combines with hydrogen to form NH_3. An excess of KOH, 40 per cent., is added. The ammonia is then distilled over into a known amount of standard acid (H_2SO_4). From the diminution of the acidity of the standard acid the amount of ammonia produced is calculated, and from this the amount of nitrogen present is estimated.

Chlorides.

The chief chloride in urine is sodium chloride, which is chiefly derived from the sodium chloride taken with the food. Sodium chloride is a useful stimulant for the renal cells. There is also a small quantity of potassium chloride present in urine.

TEST.—The urine is acidified with a little nitric acid, and silver nitrate added; a white precipitate of silver chloride is produced which is soluble in ammonia. The acid prevents the precipitation of silver phosphate.

ESTIMATION OF CHLORIDES.

Volhard's Method.—All the chlorides present are precipitated by an excess of a standard solution of silver nitrate in the presence of nitric acid. The excess of silver is then estimated in a proportion of the filtrate by a solution of potassium thiocyanate which has been previously standardised against the silver nitrate.

One c.c. of the standard solution of silver nitrate corresponds with 0·01 grm. of sodium chloride.

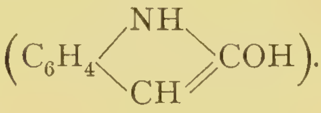
Sulphates.

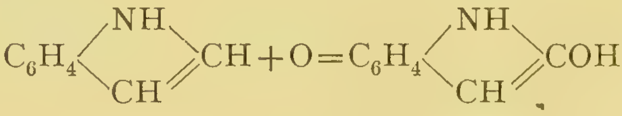
For the most part the sulphur compounds in the urine are derived from protein katabolism, for only a very small amount of inorganic sulphur enters the body in the food.

Three forms of sulphur compounds may occur in the urine :—

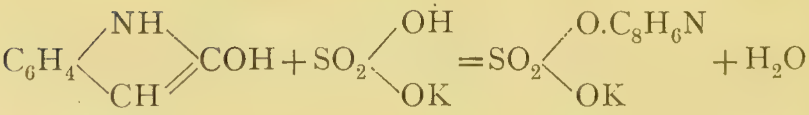
1. **Simple Sulphates of Na and K.**—These are derived almost entirely from the protein of the food (exogenous).

Test for Inorganic Sulphates.—Add a little HCl to keep the urine acid. A solution of barium chloride is added, and a white precipitate of barium sulphate produced. The HCl prevents the precipitation of barium phosphate.

2. **Conjugated or Ethereal Sulphates.**—These bodies to some extent are a measure of endogenous protein metabolism, but they are mainly due to the absorption of certain products of putrefaction from the large intestine. These poisonous products are indole, skatole, and phenol. During absorption they are so altered that they readily combine with inorganic sulphates to form relatively harmless products, which are excreted in the urine; for example, indole (C_8H_7N), which occurs in the large intestine, during absorption is converted into indoxyl . This combines with $KHSO_4$ to form indoxyl-sulphate of potassium, or indican.



(Indole) (Indoxyl)

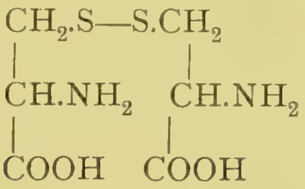


(Indoxyl) (Indoxyl-sulphate of K)

TEST FOR INDICAN.

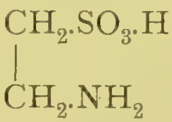
Obermayer's Test.—Add to the urine a solution of lead acetate and filter. Shake the filtrate with HCl, which contains a trace of ferric chloride and a little chloroform. Indigo-blue is produced and is dissolved in the chloroform.

3. **Imperfectly oxidised Sulphur ("Neutral Sulphur") Compounds such as Cystine.**—The neutral sulphur is probably derived from the proteins of the body (endogenous metabolism), and is an index of endogenous protein katabolism. If an animal is fed on cystine, the taurine in the bile is increased; this suggests that some of the taurine may be derived from the cystine contained in the protein molecules in the body. Keratin, for instance, is rich in cystine.



$$\begin{array}{ll} CH_2.S & \!\!\!—S.CH_2 \\ | & \quad | \\ CH.NH_2 & CH.NH_2 \\ | & | \\ COOH & COOH \end{array}$$

(Cystine)



$$\begin{array}{l} CH_2.SO_3.H \\ | \\ CH_2.NH_2 \end{array}$$

(Taurine)

Cystine occurs only in acid urine. It forms flat, colourless six-sided crystals (*vide* Fig. 57). Occasionally it forms large calculi of soapy consistency in the bladder. Cystine in the urine (cystinuria) is hereditary.

TESTS FOR CYSTINE.

1. The cystine is dissolved in a solution of caustic potash; a fresh solution of sodium nitroprusside is added; a violet colour is produced on warming the solution.

2. The cystine is dissolved in a solution of caustic potash, and a solution of lead acetate added and then boiled; there is a precipitate of the black sulphide of Pb.

The total quantity of sulphates excreted daily averages from 2 to 3 grms. Of this, nine-tenths belong to the inorganic, and one-tenth to the ethereal sulphates.

ESTIMATION OF TOTAL SULPHATES.

Dilute hydrochloric acid is added to the urine, and the mixture boiled gently. This converts the ethereal sulphates into simple sulphates.

The sulphates present are precipitated with a standard solution of barium chloride. Directly there is a trace of barium chloride in excess in the mixture, a drop of the clear fluid removed from above the precipitate, gives a cloudiness with a drop of potassium sulphate solution previously placed on a glass plate which has a black background. One c.c. of the standard solution of barium chloride corresponds with 0·01 grm. of sulphuric acid.

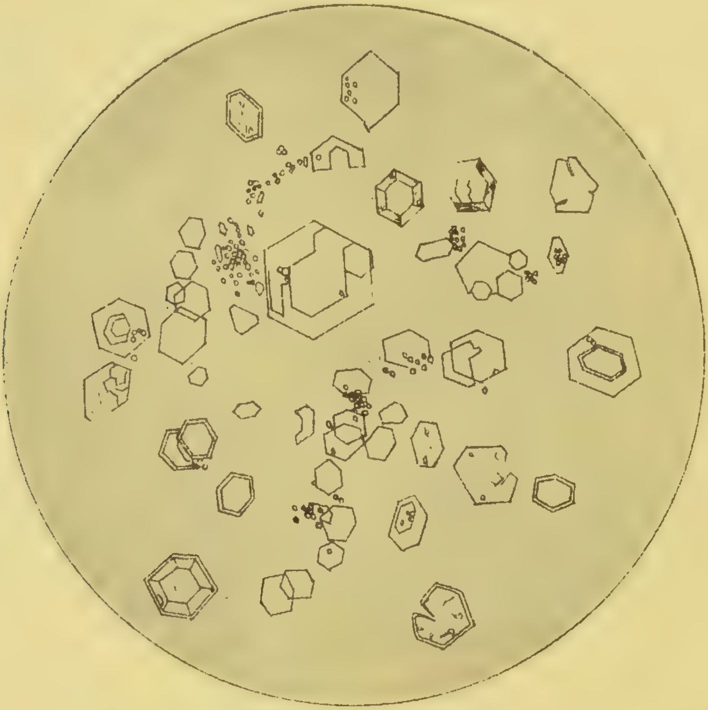


FIG. 57.—Cystine crystals. (Gibson and Russell.)

Phosphates.

The phosphates in urine are derived from the phosphorus compounds contained in the food (exogenous), and partly from the phosphorised organic compounds of the body, such as nucleoprotein, nuclein, and lecithin (endogenous). The most abundant phosphates in urine are sodium and calcium phosphate. The exact composition of the phosphates in urine depends upon the reaction of the urine. The following table shows this:

ACID URINE.	NEUTRAL URINE.	ALKALINE URINE.
NaH_2PO_4	Na_2HPO_4	Na_3PO_4
$Ca(H_2PO_4)_2$	$CaHPO_4$	$Ca_3(PO_4)_2$ (Stellar phosphate).
	$MgHPO_4$	$NH_4MgPO_4 + 6\ H_2O$ (Triple phosphate).

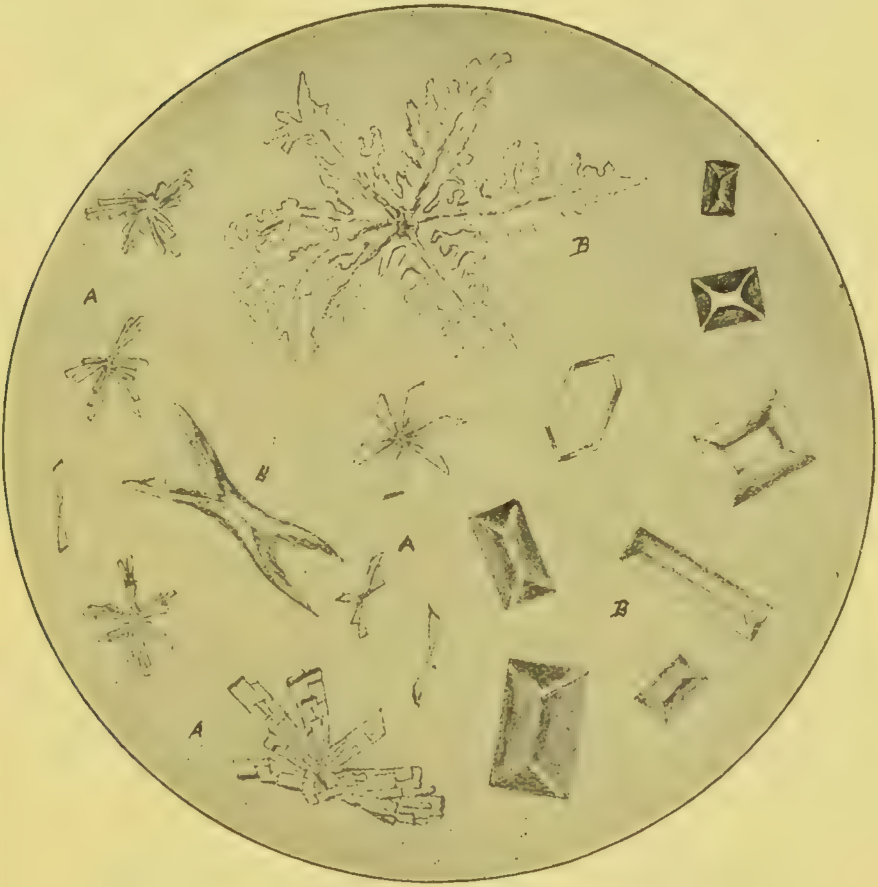


FIG. 58.—A = Stellar phosphates.
B = Triple phosphates. (Hopkins.)

TESTS FOR PHOSPHATES.

1. Earthy phosphates, *i.e.* those of Ca and Mg, may be precipitated by adding NH_3. This white precipitate is crystalline.

2. Earthy and alkaline phosphates may be precipitated by

adding HNO_3 in excess and ammonium molybdate, then boiling. A yellow crystalline precipitate of ammonium phospho-molybdate is produced.

If urine becomes alkaline, or is passed alkaline, due to the decomposition of urea into ammonium carbonate, a white precipitate of phosphates occurs. Part of this precipitate is amorphous, but crystals of stellar and triple phosphate (knife-rest crystals) occur. The precipitate of phosphates is increased on making the urine more alkaline, but is soluble in acid such as acetic acid.

Estimation of Phosphates in Urine.

To a given volume of urine a little acid sodium acetate is added (this is to prevent the occurrence of free HNO_3). The mixture is warmed to 80° C., and then a standard solution of uranium nitrate is slowly added. The phosphates are precipitated as uranium phosphate. A solution of ferrocyanide of potassium is used, to indicate when there is free uranium nitrate present in the mixture.

Free uranium nitrate with ferrocyanide of potassium produces a brown precipitate of uranium ferrocyanide. One c.c. of the standard solution of uranium nitrate solution corresponds with 0·005 grm. of phosphoric acid.

Carbonates.

The urine of vegetarians contains carbonates and bicarbonates. They are derived from the carbonates of the food and from the vegetable acids, such as citric, malic, and tartaric. These in the blood are converted into alkaline carbonates, and are excreted in the urine as such.

ABNORMAL CONSTITUENTS OF URINE.

Proteins in the Urine.—This condition is called albuminuria, and as a rule indicates disease of the cells of the urinary tubules, which results in the proteins of the plasma passing through into the lumen of the tubules. Both serum globulin and serum albumin may be present, but the latter more abundantly, as its molecule is smaller and therefore escapes the more readily. If the urine is turbid it should be filtered before the tests for protein are applied.

TESTS FOR PROTEIN IN URINE.

1. On shaking the urine a definite froth is produced, which remains for a considerable time if protein is present.

2. The urine should be made definitely acid by adding a little acetic acid, and the top of the column then boiled, a process which slowly coagulates the protein.

3. *Heller's Test.*—The urine is slowly run on to a little cold concentrated (not fuming) nitric acid in a test tube. A white precipitate in ring formation at once occurs at the junction of the two fluids. Occasionally a precipitate occurs only after some hours standing; this is due to the formation of urea nitrate crystals. A coloured ring sometimes appears at the junction of the acid and the urine, due to oxidation of colouring matters in the urine.

4. *Picric Acid Test.*—The urine is poured on to a saturated solution of picric acid; a yellow precipitate is produced, which is coagulated on being heated.

ESTIMATION OF THE PROTEIN IN URINE BY ESBACH'S ALBUMINOMETER.

The urine is poured into Esbach's tube up to the mark U, and Esbach's reagent (water with picric and citric acids) to the mark R.; the tube is then corked and tilted (not shaken), in order to mix the fluids thoroughly. A yellow precipitate occurs. The tube should be left to stand upright for twenty-four hours. The level at which the precipitate stands should then be noted, *e.g.* if the precipitate stands at the level 4, there are present in the urine four grammes of protein per litre of urine, *i.e.* 0·4 per cent.

Albumosuria.—In certain fevers, and in diseases associated with chronic suppuration, albumose appears in the urine in small quantities. Myelopathic albumosuria occurs with multiple malignant tumours of bone, and the variety of albumose present in the urine is known as Bence-Jones albumose.

TEST.—On adding the urine to concentrated nitric acid, or saturated solution of picric acid, a precipitate forms, which disappears on warming and reappears on cooling the urine.

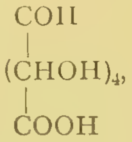
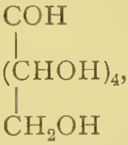
Sugar in the Urine.—As a result of hyperglycæmia (excess of sugar in the blood), sugar, chiefly dextrose, occurs in the urine. Certain poisons to the renal cells, such as phloridzin and phloretin, also cause glycosuria. The sugar most frequently present is dextrose, but sometimes lactose occurs in the urine of lactating women, and occasionally during pregnancy. Lævulose and pentose are also occasionally found.

TESTS FOR DEXTROSE IN URINE.

1. The specific gravity is between 1030–1045. In diabetes mellitus the urine is pale and has a sweetish odour.

2. *Fehling's Test.*—The urine containing the dextrose reduces Fehling's solution. The Fehling's solution should be boiled first, if it retains its blue colour the test may be proceeded with. Sometimes the tartrate which is present in Fehling's solution decomposes and reduces the cupric hydrate which is also present.

Normal urine, through the action of the urates and creatinine which are present, has a slight reducing action upon Fehling's solution.

Glycuronic acid,  $\begin{array}{c}\text{COH}\\ |\\ (\text{CHOH})_4\\ |\\ \text{COOH}\end{array}$, which is closely related to dextrose,  $\begin{array}{c}\text{COH}\\ |\\ (\text{CHOH})_4\\ |\\ \text{CH}_2\text{OH}\end{array}$, occurs in the urine after taking such drugs as camphor, chloral, chloroform, morphia, antipyrin, and antifebrin, and also reduces Fehling's solution.

Alcaptonuria, the result of abnormal protein katabolism, may occur, and the result is reducing substances in the urine. Alcapton urine does not ferment; it is optically inactive. One of the reducing substances in the urine is homogentisinic acid [$C_6H_3(OH)_2.CH_2.COOH$].

3. *Johnson's Test.*—To the diabetic urine a little saturated solution of picric acid and a few drops of 20 per cent. KOH are added. The solution becomes opaque on being heated, due to the reduction of the picric to picramic acid by the dextrose.

4. *Fermentation Test.*—To a test tube full of diabetic urine, a little yeast is added, the tube is then inverted over a trough of Hg and kept at 40° C. The urine is partly replaced by CO_2 which collects at the top of the tube, alcohol forms

in the urine, the sugar gradually disappears, and the specific gravity of the urine becomes reduced.

5. *Phenyl-hydrazine Test.* — To a test tube half full of diabetic urine a little phenyl-hydrazine hydrochloride and crystals of sodium acetate are added, and the whole boiled for half an hour. By the end of that time bundles of yellow needle-shaped crystals will have formed in the test tube. These are crystals of phenyl-glucosazone.

ESTIMATION OF DEXTROSE IN URINE.

1. *By Einhorn's Fermentation Saccharimeter.*—This consists of a glass tube shaped as in Fig. 59.

Ten c.c. of the diabetic urine are mixed with some yeast, or the powder sold commercially as zymin, which contains the active enzyme (zymase) of yeast. The apparatus is filled with this mixture, all air bubbles excluded, and fermentation allowed to proceed at room temperature. Some of the CO_2 produced collects in the upper part of the long limb of the tube, and the percentage of sugar present is read off on the empirical graduation present.

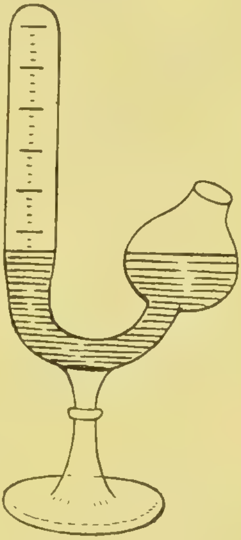


FIG. 59.—Einhorn's fermentation saccharimeter.

By Ling's Modification of Fehling's Method.—Ten c.c. of Fehling's solution (which are completely reduced by 0·05 grm. of dextrose) are placed in a large flask and boiled. One part of the diabetic urine is diluted with 9 parts of water (dilution 1 in 10) and placed in a burette. The diluted urine is slowly run into the boiling Fehling solution, and after each addition the mixture is again boiled. The blue colour of the mixture gradually disappears, and is replaced by a brick-red precipitate, which indicates that the cupric hydrate has been reduced to cuprous oxide. It is always a little difficult to determine the end of the reaction, *i.e.* when all the cupric hydrate is reduced. This, however, can be determined by the indicator, ferrous thiocyanate. If cupric hydrate is brought into contact with ferrous thiocyanate, the ferrous salt becomes oxidised and the red ferric thiocyanate produced. Drops of the indicator are placed in the wells of a white slab; when it is thought that the cupric hydrate is disappearing from the boiled mixture, a drop of the mixture is withdrawn on a glass rod and placed in the centre of one of the drops of the ferrous thiocyanate solution; if a red colour appears, more of the diluted diabetic urine is added to the Fehling solution, and the mixture boiled again, and the test repeated until no red colour is produced with the ferrous thiocyanate, showing the complete reduction of the cupric hydrate to cuprous oxide.

Suppose it requires 20 c.c. of diluted diabetic urine to reduce 10 c.c. of Fehling solution,

It therefore requires 2 c.c. of undiluted urine to reduce 10 c.c. of Fehling solution.

∴ 2 c.c. urine contain 0·05 grm. dextrose.

∴ 100 c.c. urine contain 0·05 × 50, *i.e.* 2·5 per cent.

Diabetic urine may also contain β-hydroxybutyric acid, aceto-acetic acid, and acetone, cp.—

$CH_3.CHOH.CH_2.COOH$ = β-hydroxybutyric acid.
$CH_3.CO.CH_2.COOH$. = aceto-acetic acid.
$CH_3.CO.CH_3$ . . = acetone.

β-hydroxybutyric acid does not ferment with yeast. It is lævo-rotatory. β-hydroxybutyric acid in the blood is the cause of diabetic coma.

TEST FOR ACETO-ACETIC ACID.

Add to the urine a little H_2SO_4 and shake with ether. On standing the ether rises, and contains the dissolved acetone. The ethereal solution is poured into another test tube and shaken with a solution of ferric chloride. A red colour is produced if aceto-acetic acid is present.

TESTS FOR ACETONE.

Acetone in the urine may be detected by its characteristic smell.

Legal's Test.—Add to the urine a few drops of a solution of sodium nitro-prusside (freshly prepared), and a little 20 per cent. KOH; a red colour is produced. If a few drops of strong acetic acid are added the colour becomes deeper. (Aceto-acetic acid also gives this test.)

Gunning's Test.—Add to the urine an alcoholic solution of iodine and a little strong NH_3. Iodoform and a black precipitate of nitrogen iodide are formed. The black precipitate, however, soon disappears, leaving the iodoform, which can be detected by its odour.

Bile in the Urine.—As a result of obstruction to the bile passages the bile may pass back into the lymphatics, and so into the blood (cholæmia). As a result bile salts and bile pigments appear in the urine.

Bile pigments may be detected in the urine—

1. By the colour of the urine.

2. By Gmelin's test, a play of colours produced by fuming nitric acid (*vide* p. 130).

Bile salts are most readily detected by Hay's test:—

If flowers of sulphur are sprinkled upon urine containing bile salts, the flowers of sulphur sink. This is because bile salts in solution diminish the surface tension (*vide* p. 129).

Blood may occur in the Urine through injury or inflammation of the urinary tract, or as the result of a toxæmia. If blood corpuscles are present the condition is called hæmaturia, and the blood may be detected by—

1. The colour of the urine, smoky to bright red; or it may have a dark porter colour.

2. Microscopical examination. Blood corpuscles are readily recognised; the coloured corpuscles are frequently crenated.

3. Spectroscopical examination (*vide* p. 257).

4. The test with tincture of guaiacum and ozonic ether (*vide* p. 269).

Oxyhæmoglobin and methæmoglobin (more commonly) may be present apart from corpuscles (hæmoglobinuria). This condition is due to toxic agencies, which cause destruction of some of the red blood corpuscles (hæmolysis) in the blood stream.

Occasionally, as the result of poisoning by sulphonal, alkaline hæmato-porphyrin occurs in the urine (hæmato-porphyrinuria). It is iron-free hæmatin, and can be detected by the dark colour it produces, and by the spectroscope.

Pus (dead round cells) occurs in the urine as a result of suppuration in connection with the urinary tract. It forms a creamy white precipitate upon standing, and the cells can be seen with the microscope.

Mucus is frequently present with the pus cells (muco-pus). On KOH 20 per cent. being added a ropy precipitate is produced.

SECTION XI.

THE NERVOUS SYSTEM.

CHAPTER XXXVI.

THE NEURONE.

General Structure.—The functional and morphological unit in the construction of the nervous system is the neurone. The neurone is the highly differentiated nerve cell.

Taking, as the example of a neurone, a multipolar nerve cell of the anterior cornu of the spinal cord, a neurone consists of a cell body or perikaryon, and one or more fine processes projecting from it.

The cell body or perikaryon in the case of the anterior cornual cell is multipolar in shape. In the centre of it there is a nucleus, which possesses a well-defined and large round nucleolus. Generally the nucleus of a nerve cell is relatively poor in chromatin. In some cases the cell body also contains a small mass of pigment which is of a fatty nature.

From the angles of the cell body are given off the nerve cell processes. In the case of the multipolar cell the number of cell processes corresponds with the number of angles or poles possessed by the perikaryon. The processes given off from all the angles are, however, not of an identical structure. The majority of the processes are short and somewhat thick at their attachment to the cell body, but diminish rapidly in calibre as they are traced away from the cell body. The processes have a rough outline, due to the presence of fine prickles or "gemmules" upon them. These processes, as they are traced away from the perikaryon, branch rapidly in a dendritic or tree-like fashion; hence they are called dendrons, and their small subdivisions dendrites. They were formerly called after their discoverer, the "protoplasmic processes of Deiters."

The other variety of nerve process, of which only one is given off from every nerve cell, is called the axon, the axis cylinder process, or the neuraxis. The axis cylinder differs in certain important particulars from the dendrons.

First, the dendrons rapidly branch, whilst the axis cylinder usually travels a considerable distance (in the case of the axis cylinders passing to the muscles of the sole of the foot as much as one metre) before breaking up into its terminal ramification. This terminal subdivision in the case of the axis cylinder is called a telodendron.

Secondly, the dendron is rough and rapidly diminishes in calibre as it is traced to its termination, whereas the axis cylinder has a smooth outline and diminishes very slightly in its course to its termination.

Thirdly, the dendron is naked right to its termination, whereas the axis cylinder, as it is traced away from its point of origin from the nerve cell, usually becomes enveloped in one or two coats.

Fourthly, the dendron gives off irregular branches, whereas the axis cylinder usually gives off minute branches only, without suffering any diminution in calibre thereby; these branches are called collaterals.

Microscopic Structure.—When the nerve cell and its various processes are stained by suitable reagents, other important features of its microscopic anatomy become apparent.

1. Running throughout the perikaryon and the nerve processes there is a delicate arrangement of exceedingly fine fibrils, called neuro-fibrillæ. They may be seen stretching through the perikaryon, and forming therein a very complex reticulum. They are also present in the dendrons; whilst the axis cylinder is composed almost entirely of these fine fibrillæ, bound together by a very small amount of inter-fibrillar substance. It is said that these fibrillæ can be traced from the dendrons through the perikaryon, and out again by the axis cylinder, and it is stated that the axis cylinder receives contributions of fibrillæ from each of the different dendrons.

The fibrillæ were first described by Max Schultze. They were formerly believed to be artefacts, *i.e.* that they were not normal structures of the cell, but appearances produced by the reagents used in staining the cells; but they have been demonstrated in the nerve cells of certain invertebrates.

According to some authorities, the neuro-fibrillæ are minute hollow tubes, and certainly some sections of nerves appear to support this view (Schäfer).

As just described, it will be seen that the distribution of the neuro-fibrillæ is limited to the neurone, and that they do not transgress beyond the borders of that structure; but it is well to remember that certain authorities do not agree with this view. Apàthy, from his researches upon the nervous system of the invertebrates, concludes that the neuro-fibrillæ pass from one cell of the nervous system into another, and that, in fact, the neuro-fibrillæ form a delicate reticulum throughout the whole of the nervous system. Bethe supports this view in the case of the vertebrate animals.

The neuro-fibrillæ are structures quite separate from the ordinary spongioplasmic network of the nerve cell, and are not due to the spongioplasm arranged in the form of delicate long fibrillæ.

2. When the nerve cell is stained with methylene-blue, either by the *intra vitam* method of Ehrlich or the method of Nissl, certain important structures are demonstrated as scattered throughout the perikaryon and in the protoplasm of the larger dendrites. These structures are called the "granules of Nissl," and are of great physiological importance. They are spindle-shaped bodies, which stain an intense blue with methylene-blue (or toluidine-blue); they lie in the meshes of the neuro-fibrillæ of the perikaryon. One or two of these granules may be seen to be applied to the nuclear network, and these are usually helmet shaped. They are also found in the dendrons, but these are spindle-shaped. They are absent from the axis cylinder and from the dendrites.

These granules are of great importance, because they undergo certain changes during the occurrence of different physiological and pathological states, and are an indication of the condition of the cell.

3. *The Axon Hillock.*—This is that portion of the perikaryon from which the axis cylinder is given off. It differs somewhat in appearance from the rest of the perikaryon, particularly in the fact that in this area there are

no Nissl granules. Probably this is due to the accumulation of neuro-fibrillæ which pass into the axis cylinder in this neighbourhood.

Varieties of Neurones.

The neurones are classified into various subdivisions according to the number of branches to which they give rise.

I. In the first group are those which possess no axis cylinders, although they are usually described as nerve cells. The group of cells is called the **apolar neurones.** Examples of these cells are found in the cerebral cortex covering the hippocampus major, and also in the retina. In the latter situation they are called amacrine cells. These cells are found in the inner nuclear layer of the retina, and, although they give off fine processes of their protoplasm into the inner molecular layer, yet they do not give rise to an axis cylinder.

II. In the second group are the **unipolar nerve cells.** These cells are plentiful in the nervous system of the invertebrates, and usually give off a single process, which rapidly subdivides. In the mammalian nervous system unipolar cells are found in the spinal ganglia. These cells are rounded or spherical in shape, and contain a distinct well-defined nucleus and numerous Nissl granules. They give off a single process, which is, as a rule, coiled spirally upon the surface of the perikaryon, and which ultimately divides in a T-shaped manner into two processes, both of which, from the histological point of view, must be considered to be axis cylinders. The T-shaped subdivision is called the T-shaped junction of Remak. This variety of unipolar cell is developmentally bipolar.

True unipolar cells are also found amongst the cells composing a sympathetic ganglion. The perikaryon of these particular cells is usually pyriform in shape.

III. The third group comprises the **bipolar nerve cells.** True bipolar nerve cells are found in the spinal ganglion of fishes and in the vestibular (or Scarpa's) and cochlea (or spiral) ganglia in mammals. These cells are somewhat ellipsoidal in shape, and from the poles nerve processes are given off; each of these nerve processes is histologically an axis cylinder.

The unipolar nerve cell of the mammalian spinal ganglion is, as already stated, the bipolar cell during the earlier stages of its development, with a structure exactly as that just described as characteristic of the spinal ganglion of the fish. During development, however, the perikaryon leaves the course of its two branches, and passes to the side (usually to the side nearest to the periphery of the ganglion), and, ultimately passing further away, its two branches are brought into apposition and become fixed in the proximal parts of their course to form a single process. Its double nature, however, is evident from the fact that, histologically, neurofibrillæ can be traced from one process along the single process into the perikaryon, then out of the perikaryon, along the single process again into the other branch of the T junction.

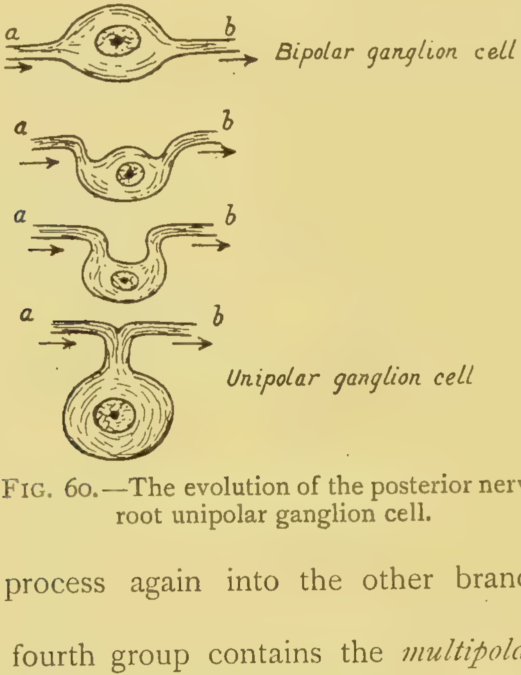


FIG. 60.—The evolution of the posterior nerve root unipolar ganglion cell.

IV. The fourth group contains the *multipolar nerve cells*. This group of cells is characterised by possessing numerous nerve processes, and it is in this group that the characteristic distinction of axons and dendrons are found. Examples of this group are :—

(*a*) The *multipolar nerve cells* of the anterior cornua of the cord, sometimes called the anterior cornual nerve cells.

(*b*) The *pyramidal cells* of the cerebral cortex. Each cell is pyramidal in shape. From the middle of the base is given off the characteristic axis cylinder, whilst from each of the angles the branching dendrons arise. These cells are found in large numbers throughout the whole cerebral cortex.

A large variety—the cell of Betz (or of Bevan Lewis), is found in the cortex of the Rolandic or sensori-motor area.

(*c*) *The cells of Purkinje.*—This variety of cell is localised in the cortex of the cerebellum. It is a large, flask-shaped cell which gives off from its base a single axis cylinder, and from the apex it gives rise to dendrons which branch so abundantly as to form what is sometimes called the cerebellar forest.

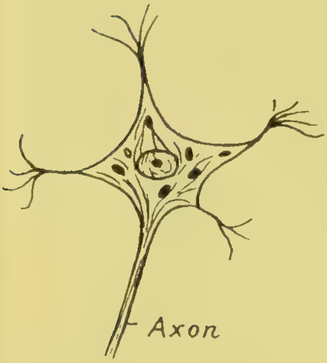


FIG. 61.—A multipolar nerve cell.

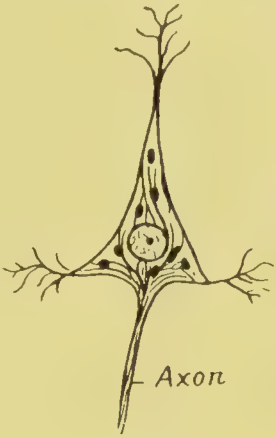


FIG. 62.—A pyramidal nerve cell.

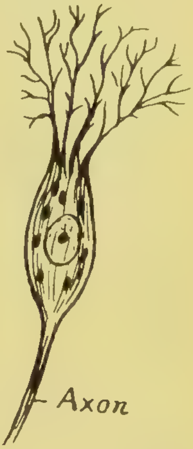


FIG. 63.—A flask-shaped cell of Purkinje.

So far the cells that have been described possess long axis cylinders, but there is a second series in which the axis cylinder is short and rapidly branches. Golgi therefore has divided nerve cells into two groups—

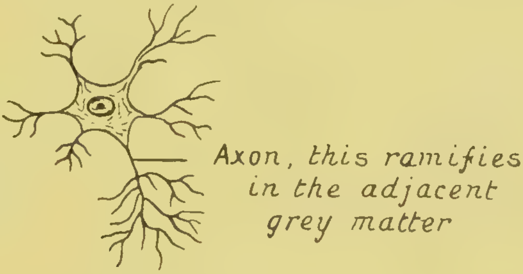


FIG. 64.—A Golgi cell.

(1) The radicular, or root cells, of which all the cells mentioned above are varieties; and (2) the short, or associational cell, sometimes called the Golgi cell, in which the axis cylinder effects a rapid branching. They are found in the grey matter of the brain and spinal cord.

Development.—The nerve cells are developed from the cells of the epiblast. These cells are present in the walls of the neural canal at the time of its formation, and, before this, in the floor and sides of the medullary groove, the analogue of the central nervous system. Earlier than this they were present in the median thickening of the epiblast known as the medullary plate. The neurones of the sympathetic ganglia come, it is believed by the majority of embryologists, from the cells of the neural crest—a thickening of the epiblast at the point where the medullary groove becomes continuous with the embryonic epidermis, before the groove has become closed to form the neural canal.

In the first stage of their existence these nerve cells are spherical in shape, and possess no nerve processes. Further, they are capable of multiplication, and multiply by karyokinetic division. These cells are called germinal cells. The next stage in their development is the protrusion of the axis cylinder, so that the cell becomes pyriform in shape. This stage is called the neuroblast stage. Later still, the protoplasmic processes of Deiters are formed as outgrowths of the neuroblast. These protoplasmic processes are branched from the commencement.

In the case of the spinal ganglion cells, the process growing into the central nervous system is the first process to develop, so that it is usually considered to be the axis cylinder; whilst the process which passes to the periphery develops later, and is regarded as being of the nature of a dendron.

From the simple variety of nerve cell with localised and single branching, the complex nerve cell of the adult is developed by a process of growth. It is interesting to note that, during this process of development, the nerve cell repeats that unique process, characteristic of all embryological processes; that is, that it climbs up its genealogical tree, for it repeats the phylogenetic development, as shown by a study of the nerve cells of fishes, amphibians, and reptiles, and also by the recognition of the gradually increasing complexity of branching observable in these different animals in the order named.

It appears to be a definite truth that the higher the grade of branching seen in a nerve cell, the higher in the zoological scale is the animal from which it came, and the more highly developed is the nerve cell.

A nerve cell, when it has once reached the highest stage of development, no longer continues to divide and multiply.

The Nissl Granules and their Significance.

It has been already pointed out that, when nerve cells are stained by any of the basic aniline dyes, such, for example, as methylene- or toluidine-blue, these nerve cells then exhibit, scattered throughout their substance, small granules, which have a special affinity for these dyes, and stain deeply with them. These bodies are usually spindle shaped, and are scattered about in the cytoplasm of the perikaryon of the nerve cells, lying between the delicate neuro-fibrillæ; also, as was pointed out, there are, as a rule, one or two helmet-shaped granules lying in close apposition to the nucleus of the cell.

It has been a point of discussion as to whether the granules, as shown by methylene-blue staining, actually exist as such in the living nerve cell, or whether they are not artifacts,—that is, a post-mortem phenomenon produced by the methods of fixing and staining employed for their demonstration. The view generally accepted, however, is that such bodies do exist in the nerve cells. Whether they do or do not does not matter greatly, the essential point to remember being that, if a normal nerve cell is stained according to certain methods by methylene-blue, these bodies then appear sharply defined and very distinct, and that, if a nerve cell exhibits appearances differing from this normal character, when stained according to the same method, then this latter nerve cell is either pathological or differs in some physiological respect from the nerve cell previously referred to.

The chemical nature of these granules is unknown; but it is believed that they are nucleo-protein in nature, and that they contain iron. Since they take up basic dyes with such great affinity and readiness, they must be acidic in nature.

Under certain conditions these granules cease to be so well defined, and become broken up into fine particles. In these circumstances, the nerve cell when treated with methylene-blue becomes diffusely stained, and the whole cell body becomes of a blue colour. This condition is termed "chromatolysis," and chromatolysis occurs under the following conditions:—

1. If the axis cylinder of any nerve cell is divided, the

Nissl granules of that particular nerve cell undergo chromatolysis. This process is spoken of as "Nissl degeneration."

2. If any nerve cell has been particularly active the Nissl granules of that nerve cell undergo chromatolysis. For example, Hodge has shown that the Nissl granules present in the perikaryon of the cells of the spinal ganglia of the swallow are distinct before that bird has commenced an active day's flying; but that, after the day's work is completed, the Nissl granules are absent, they having undergone chromatolysis.

3. After the anterior cornual cells have been very active their granules also undergo chromatolysis (Gustav Mann).

4. During asphyxia chromatolysis also occurs.

5. Chromatolysis occurs under the influence of certain poisons, notably phosphorus.

6. Chromatolysis occurs during the specific fevers; apparently this results from the pyrexia.

7. Warrington has shown that severance of the posterior nerve roots of a spinal nerve causes Nissl degeneration, or chromatolysis of the nerve cells of the corresponding anterior cornua. This is considered to be a "disuse atrophy."

From a histological standpoint, because of the great affinity with which these bodies take up stains like methylene-blue, they are said to consist of "chromatoplasm." From the physiological point of view, Marinesco has named the material of which they consist "kinetoplasm," to indicate that they are a storehouse of energy, and that their disappearance (or the process of chromatolysis) is associated with the liberation of nerve energy.

Conduction in the Neurone.

The essential function of the nervous system, and also of each of its individual units, is that of conduction. Nerve impulses are conducted through nerve cells and along their different branches. But this conduction is governed by certain laws, and the laws appear to be these—

(1) That conduction of a nerve impulse in an axis cylinder is from perikaryon to periphery; and (2) conduction of an impulse in a dendron is from periphery to perikaryon.

These laws are certainly correct for the motor nerve cell; and if the view is accepted, that the branches of a posterior nerve root ganglion cell are dendron and axis cylinder respectively, the axis cylinder joining the perikaryon to the cord, and the dendron joining the perikaryon to the periphery, then these laws also apply to the afferent neurone.

These facts are grouped together under the term "the law of axipetal conduction." Knowing the arrangement of any particular series of nerve cells, and remembering this law, the course of any given nerve impulse can be deduced.

Further, since nerve cells of an afferent function communicate with efferent nerve cells by the axis cylinder of the first mentioned, arborising round (but not anastomosing with) the dendrites of the second, it follows that the path of conduction of nerve impulses is from afferent to efferent nerve cells. This is the expression of a law known as the *Law of Forward Conduction* of James.

NERVE DEGENERATION.

Effects of Section of the Axis Cylinder.

Section of the axis cylinder is succeeded by the appearance of several phenomena. These may be classified as—

1. Changes in function.
2. Physiological changes.
3. Histological changes.
4. Chemical changes.
5. Extraneural changes.

The Changes in Function are as follows. The function of the nerve fibre, considered as a conductor of nerve impulses, is completely destroyed. If the nerve severed is a sensory nerve, no sensory impulses are conducted along it; that is, there is complete anæsthesia in the area formerly supplied by the nerve. If a motor nerve is divided, the muscles, formerly controlled and activated by these nerve impulses, are paralysed, and can no longer be called into action, either by impulses arising in the cerebral cortex or as the result of peripheral excitation.

The Physiological Changes are manifested in—

1. An increase of excitability at the point of section, and in its immediate neighbourhood, owing to the "demarcation current" (Du Bois-Reymond), or "currents of injury" (Hermann), set up in the nerve fibre as a result of its section. These changes are, however, but transient, and are rapidly succeeded by

2. Loss of irritability and of conductivity in the severed portion of nerve fibre. According to the Ritter-Valli law, this loss of irritability occurs first in the central end of the divided nerve, and then progresses in a wave towards the peripheral endings; though, according to some physiologists, the failure of excitability occurs gradually but simultaneously in all portions of the divided nerve fibre.

The Histological Changes which take place "in the neurone" on section of its axis cylinder must be described under three headings:—

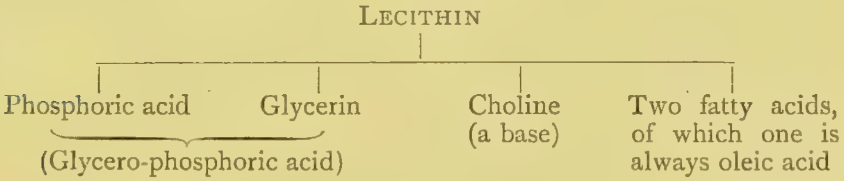
1. The changes which occur in the peripheral portion of the divided nerve fibre. These changes are grouped together under the term "Wallerian degeneration." They are the natural changes which follow severance of a process belonging to a cell; in this case the process of a highly specialised cell is cut off from its nutritive or trophic centre, that is, the nucleus of the cell of which the process is a part. The histological phenomena commence about twenty-four hours after the establishment of the lesion, and are ushered in by fragmentation of the medullary sheath of Schwann, which subsequently becomes converted into oily droplets. Simultaneously, the axis cylinder becomes wavy and varicose, and at the same time, or even earlier, shows slight variations in staining reactions to the normal axis cylinder. Later it becomes broken up into a series of minute isolated granules. These changes are said to occur first at the site of section, and then to proceed to the periphery. The nuclei of the primitive sheath multiply, and they invade the degenerating nerve. The multiplied cells of the neurilemma, later in the degeneration, play the part of scavengers, and remove the destroyed sheath of Schwann and the axis cylinder, leading to the conversion of the degenerated nerve into tubes of neurilemmal cells, filled with granular multinuclear protoplasm, and surrounded by proliferated connective-tissue cells.

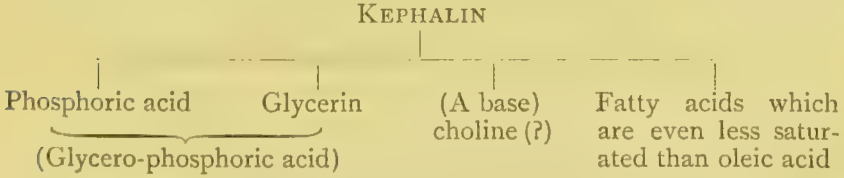
The changes occurring after lesion of a non-medullated nerve fibre are the same in character as those described above. The axis cylinder becomes converted into isolated granules, and finally absorbed by the neurilemmal cells which have previously multiplied. It is obvious that the oily droplets which result from the degeneration of the fatty sheath of Schwann are absent.

2. Similar degenerative changes take place, although at a very much slower rate, along the central part of the cut nerve.

3. Certain changes occur in the nerve cells from which these axis cylinders are derived. In the case of motor nerve fibres, the motor cells undergo changes which are termed Nissl degeneration. Within from twenty-four to forty-eight hours of the section the granules of Nissl undergo chromatolysis; they become less defined and more diffuse, so that when the cell is treated with methylene-blue the whole perikaryon becomes diffusely stained. This process apparently commences near the axon-hillock, and from this extends through the whole perikaryon, first immediately around the nucleus, and finally invades the larger dendrons. The cell body meanwhile becomes swollen and the nucleus eccentric; later it becomes atrophied and rounded. These processes continue for about fifteen days; when they cease the cell undergoes a process of regeneration, and later returns to its normal appearance and condition. Division of a spinal nerve between the spinal cord and the posterior root ganglion causes only a slight degree of chromatolysis of the ganglion cells; if, however, the afferent nerve is divided in that portion beyond the ganglion, the cells in the ganglion undergo chromatolysis and eventually atrophy.

The Chemical Changes can be readily understood when the chemistry of the medullary sheath of Schwann and of the axis cyclinder is recalled. These portions chiefly consist of substances called lipoids. The lipoids present are cholesterin, cerebrosides, lecithin and kephalin, and they are found in greater abundance in the axis cylinder itself than in the medullary sheath. When degeneration occurs, the phosphatides present, lecithin and kephalin, are hydrolysed into their cleavage products, according to the following schemes:—


LECITHIN
Phosphoric acid
Glycerin
Choline
(a base)
Two fatty acids, of which one is always oleic acid
(Glycero-phosphoric acid)


KEPHALIN
Phosphoric acid
Glycerin
(A base)
choline (?)
Fatty acids which are even less saturated than oleic acid
(Glycero-phosphoric acid)

It has been suggested (Marinesco) that these hydrolyses are due to the action of enzymes produced by the neurilemmal cells; but, whatever the cause, it is a fact that hydrolysis does take place. As a result, the amount of free fatty acid and choline in the degenerated nerve increases for a few days (usually about from eight to ten), and then diminishes finally to disappear, owing, of course, to the fact that these substances are then absorbed by the lymphatics. The amount of phosphorus in the degenerated nerve diminishes from the moment of section.

These changes are of great interest and importance from the standpoint that, in those diseases in which destruction of nervous tissue actually occurs, *e.g.* in general paralysis of the insane, there is a considerable amount of choline in the cerebro-spinal fluid and in the blood, owing to absorption of this product from the degenerated elements (Mott and Halliburton). On the other hand, where the disease is merely of functional origin there is no choline in the cerebro-spinal fluid, because in such disease no destruction of nerve cells occurs (*vide* p. 53).

The staining reactions utilised in the histological investigations of degenerated nerves and tracts depend upon the chemical phenomena described above. Thus Marchi's reaction, staining with osmic acid, is due to the reduction of the tetroxide of osmium to the lower black oxide by the unsaturated fatty acids freed in the phosphatide hydrolysis. It is obvious, therefore, that the degenerated nerve fibres will only give the reaction so long as these unsaturated fatty acids remain unabsorbed, *i.e.* within a few weeks of the lesion. Similarly, the Weigert-Pal method of staining, whereby medullated nerves stain a deep blue, but non-medullated nerves and degenerated nerves after sclerosis (*i.e.* removal of the chemical products of degeneration), and also the grey matter, remain unstained, is believed to depend upon some change in the lipoid constituents of the nervous material (*vide* p. 487).

The Extra-Neural Changes are those which occur in the other structures outside the particular neurone which is damaged. Thus, when the motor nerve to a muscle is divided, not only is that particular muscle paralysed, but there is gradual atrophy of that muscle, due to the removal of the trophic influences exerted upon that muscle by the motor nerve. Also, when a particular nerve fibre is severed, which formerly conducted impulses to other neurones, then these other neurones undergo a series of changes called "disuse atrophy." The chief manifestations of this particular form of degeneration are—

1. Diminution of the calibre of the axis cylinder.
2. Shrinkage of the nerve cell; and occasionally
3. Chromatolysis.

Such a series of changes takes place in the cells of the anterior cornua of the grey matter of the spinal cord, upon section of the posterior roots belonging to the same segments of the cord (Warrington).

REGENERATION OF NERVE.

The process of degeneration of the nerve fibres is succeeded, under suitable conditions, by *regeneration.* Under regeneration are included all those phenomena ending finally in the complete restoration of continuity and function of the divided axis cylinder.

The actual restoration of the axis cylinder is preceded by the exhibition of a deal of activity upon the part of the neurilemmal cells of the isolated portion of nerve. The nuclei of these cells actively multiply, even at a very early stage in the process of Wallerian degeneration, as has been already pointed out. Still later they, together with emigrated leucocytes, remove the products of degeneration of the medullary sheath and axis cylinder. They then become spindle shaped, and, joining together end to end, constitute the so-called "embryonic nerve fibre." These cells, however, do not represent the regenerated axis cylinder; they are simply the neurilemmal sheath of that structure, which at a later date grows down into the centre of them. For some time after the appearance of the axis cylinder, however, the neurilemmal sheath retains an abnormal thickness; later, however, it shrinks to its normal thickness.

The source of the new axis cylinder is at the present time a subject of some controversy. There are two main views upon the subject—

(1) That the new axis cylinder is a down growth from the central end of the divided nerve, and grows down into the tunnel made by the neurilemmal cells of the previously degenerated fibre.

(2) That the new axis cylinder is formed *in situ* from cells in the peripheral portion, and subsequently grow up towards the spinal cord. This is the view of "autogenetic regeneration," which supposes that new nerve fibres develop from the neurilemmal sheath of the nerve fibres which have degenerated.

I. The *first view* is the older view upon the subject, and at the present time is the generally accepted one. It was first described by Waller, in 1850, and has been supported during recent years by the work of Halliburton and Mott, Howell and Huber, and others. The following are the chief observations adduced in its favour:—

1. Lugaro has shown that, if the lower portion of the spinal cord is removed, and the nerves connected with it cut, no regeneration occurs. This shows that the growth of nerve fibres depends upon the activity of nerve cells in the central nervous system from which the fibres originally grew.

2. Cajal and Marinesco have both described histological appearances supporting the theory. They have found that the peripheral end of the central stump of nerve grows downward into the degenerated nerve. This new axis cylinder may pursue a long and tortuous course, becoming much convoluted and twisted upon itself, but it ultimately reaches the peripheral stump and travels along this to the periphery. The growing fibre is terminated by an olive-shaped swelling, the "incremental zone," exactly similar to the swelling found at the growing end of embryonic developing axis cylinders. The greater the obstacles opposed to the growth of the regenerating axis cylinder, the greater time elapses between union and restoration of structure and function in the degenerated nerve.

3. If the upper cut end of the peripheral portion of nerve is enclosed in a sterilised rubber cap, no regenerated axis cylinders can be found in the degenerated nerve (Halliburton, Mott, and Edmunds). In this way surrounding nerves cannot invade the peripheral shielded portion. The lower portion degenerates and *no* regeneration occurs. These investigators have successfully transplanted a piece of nerve on to the peritoneal surface of the stomach, where it is not invaded by other nerves, and they find that no regeneration occurs.

These facts argue against a peripheral origin of the new axis cylinders.

4. After regeneration has occurred in a divided nerve, if the nerve is again divided on the central side of the original cut (Langley and Anderson), degeneration occurs in all the new fibres, showing that they are all under the nutritive control of the nerve cells in the cord and in the posterior root ganglia. If, however, the nerve is divided a second time between the original cut and the periphery, degeneration takes place peripheral to the second section. Now, the direction of degeneration is the direction of growth, and these facts would therefore appear to support the view that regeneration takes place in the direction of from centre to periphery (Halliburton and Mott).

5. If the assumption that regeneration is carried out by the same forces as the growth of the axis cylinder in the embryo is correct, then the experiments carried out by Ross Harrison upon the growth of the nerve fibres in the developing frog are of great interest. In these experiments he removed small pieces of the primitive nerve tube which forms the central nervous system and small portions of the surrounding tissue from frog embryos. These he kept alive and examined in a drop of lymph. Under certain conditions they remained alive for some considerable time. From the primitive nerve cells he observed nerve fibres growing out into the surrounding parts. Moreover, each fibre became finely fibrillated, and had at its free end a small swelling, very like the swelling present at the end of a regenerating nerve fibre, which exhibited active amœboid movements; and, growing outward, increased the length of the fibre at the rate of 1 micro-millimetre ($\frac{1}{1000}$ mm.) in every one or two minutes.

In order that the regeneration may proceed rapidly and expeditiously, the following conditions must appertain :—

(*a*) The central and peripheral ends of the divided nerve should be brought into apposition. This union should preferably be direct, *i.e.* the central stump should be joined directly to peripheral nerve; but if this condition cannot be realised the ends should be joined by the interposition either of a piece of catgut or of a piece of nerve from the same or another animal. The results are equally good in either case, and Marinesco and Kilvington have shown that the new intervening portion of nerve is absorbed before regeneration occurs, and offers no advantage over catgut union. If a cut end is sutured to an uninjured longitudinal surface no regeneration takes place (Kilvington); the surfaces should be freshly cut before apposition.

(*b*) If this union is not performed, new axis cylinders invade the degenerated nerve from the central stump of other nerves in the neighbourhood which have been divided in the course of the operation. There would, however, appear to be some chemo-tactic influence governing the course of the regenerating fibres, for the regenerating fibres of the central stump of a divided nerve always tend to seek the degenerated peripheral portion of the same nerve in preference to the degenerated portions of other nerves in the neighbourhood. If, on the other hand, the central stump of one divided nerve is sutured to the peripheral cut end of another nerve, then the regenerating fibres of the stump take the new course along the degenerated nerve to which it is sutured. Thus Ballance united part of the spinal accessory nerve to the peripheral end of the facial, regeneration occurred, the patient recovered the use of the previously paralysed facial muscles, with, however, synchronous lifting of the shoulder.

That union leads to regeneration of nerve fibre, although usually the case, is not entirely the truth. The medullated nerve fibres of the spinal cord do not appear to regenerate after section, and section of the posterior roots between the spinal ganglia and the cord leads to degeneration of the fibres of the posterior columns of the cord, without apparent subsequent regeneration. Apparently the neurilemmal cells, which undergo certain changes during the nerve regeneration, and which are absent from the nerve fibres of the cord, are of great nutritional value and importance in the process of regeneration.

II. The *second or autogenetic regeneration view* is supported—

(*a*) By the observations of Bethe, who claims that the peripheral portion of nerve becomes excitable before union with the central end occurs. In his experiments, however, the possibility of new nerve fibres growing into the degenerated portion of nerve from other nerves, divided during the operative procedures, was not guarded against, and he himself has weakened his position by maintaining that this "autogenetic regeneration" is confined to young animals, and is not the usual mode of regeneration in the adult, a supposition which, to say the least, it is difficult to maintain: and

(*b*) By the clinical observations of Kennedy, who maintains that the rapid return of sensation (in some cases in a few days) after section is an evidence of peripheral regeneration. These observations, however, depend entirely upon the patient's own statements, and are entirely contradicted by the observations of Head upon himself. This observer found no early return of sensation, and the date at which such sensation reappeared coincided pretty closely with the times noted in animals at which histological evidence of regeneration could be obtained.

The postulate, then, regarding nerve regeneration is, that nerve regeneration commences from the nutritive centre of the neurone, *i.e.* from the nucleus, and that therefore the regeneration always proceeds from centre to periphery.

The Weigert-Pal method (modified) of staining the central nervous system:—

1. Pieces of nerve tissue are hardened in Müller's fluid (potassium bichromate 2½ parts, sodium sulphate 1 part, water 100 parts).
2. They are then placed in alcohol, embedded in celloidin, and cut; or soaked in gum, frozen, and cut.
3. The sections are then washed in water and then transferred to Marchi's fluid (Müller's fluid 2 parts, osmic acid 1 per cent. 1 part) for a few hours.
4. They are then well washed in water.
5. Transferred to acid hæmatoxylin (logwood, alcohol, acetic acid) for about 12 hours, until quite black.
6. The sections are then washed with water.
7. Transferred to a ¼ per cent. solution of potassium permanganate for 5 minutes.
8. The sections are then rinsed in water.
9. Transferred to Pal's bleaching solution (sodium sulphite, oxalic acid, water) or to a dilute solution of sulphurous acid. The bleaching process is to be carefully watched. (Grey matter is most bleached, sclerosed white matter is yellow, medullated nerve-fibres are blue-black.)
10. The sections are then washed in water, passed through absolute alcohol (with or without eosin), cleared with xylol, and mounted in balsam.

CHAPTER XXXVII.

THE REFLEX.

Conduction across the Synapse.

As already mentioned, the afferent nerve fibre communicates by arborisation with the dendrites of motor neurones, and, according to James' law of forward conduction, conduction of nerve impulses takes place across the junction. This junction is called "the synapse." Synapses occur wherever grey matter is present, and conduction across synapses occurs under the following conditions:—

1. In the reflexes, when the nervous impulse is passing from the afferent to the efferent side of the nervous system;
2. In the conduction of afferent impulses up the cord to the brain;
3. In the conduction of motor impulses down the cord from the brain; and
4. In the conduction of efferent impulses from the cord along the sympathetic nerves.

A similar type of conduction of a nervous impulse is noted in the transmission of the motor nerve impulse to the voluntary muscle across the motor end organ.

Conduction of the nerve impulse across the synapse differs somewhat from conduction of a nervous impulse along a nerve trunk. The chief differences are the following:—

1. The conduction takes a longer time in passing through the synapse than through a piece of nerve trunk of corresponding length; that is, conduction at the synapse is slower than conduction along a nerve trunk.
2. Conduction through a synapse is much more readily fatiguable than conduction along a nerve trunk.
3. Conduction through a synapse is more easily affected by drugs than conduction through a nerve trunk. Thus, as Langley and Dickinson showed, nicotine in dilute solution

prevents conduction at the synapse, although it has no effect on conduction along a nerve trunk.

4. Conduction through a synapse usually proceeds in one direction only, according to the law of forward conduction,—that is to say, in the case of the afferent nerves, from afferent to efferent neurones, or from afferent neurones to higher parts of the brain, and consequently it is a much more difficult matter to get reversed conduction through a synapse than it is to get reversed conduction along a nerve trunk.

5. Conduction through a synapse is readily abolished by absence of oxygen; whereas absence of oxygen has very little effect on conduction along a nerve trunk, unless the oxygen supply is cut off for a considerable length of time.

THE REFLEX.

By reflex movement is meant the transformation of afferent nerve impulses into efferent nerve impulses. That is to say, reflex movement is the chain of events exhibited when, in response to some stimulation of an afferent nerve fibre, a motor or secretory response is obtained.

From the definition it at once follows that, for every reflex movement there must be—

1. A receptive organ connected with an afferent nerve.
2. An afferent neurone entering into connection with an efferent neurone.
3. An efferent neurone controlling an organ which produces activity.

In other words, the reflex arc must consist of at least two neurones,—the afferent and the efferent neurones; which, of course, must be connected together at a synapse, and therefore the reflex arc must, at one place at least, pass through grey matter, because synapses occur only in grey matter. Further, there must be an organ in which the efferent neurone produces activity, and this is usually called the effector organ; whilst the organ where the stimulus induces activity in the afferent portion of the reflex arc is called the receptor organ.

The simplest reflex arc consists of three neurones,—the afferent neurone connected with the receptor organ, the efferent neurone connected with the effector organ, and a third neurone interposed between the afferent and efferent neurone, which is called the "connecting neurone."

Using Sherrington's nomenclature, all that portion of the reflex arc up to the efferent neurone is called the "afferent arc," the efferent neurone is called the "efferent arc."

A cardinal property of the reflex is this, that the reflex is a response produced entirely independently of the cerebral cortex, that, in fact, the individual may be entirely unconscious of its production. In studying the reflexes in the cases of animals, it is therefore the custom, first of all, to prepare the animal for experiment by converting it into what is termed "the spinal animal," by dividing the cord from the higher parts of the brain and then maintaining physiological life by artificial respiration. This is a necessary procedure, for otherwise the brain would exert a controlling action upon the various reflexes, and so would vitiate the reflexes produced by experimental manipulation.

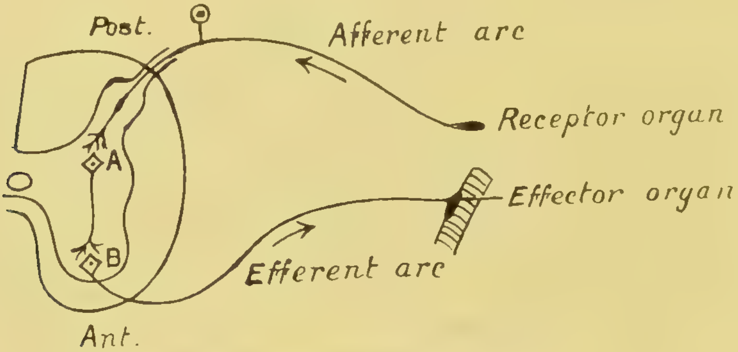


FIG. 65.—Diagram of the reflex arc.

A and B are synapses.

In such an animal it has been shown that it is possible to get particular motor responses on stimulating particular nerves. Thus, in the "spinal dog," stimulation of the foot (tickling) produces flexion at the knee, hip, and ankle (the flexion reflex); stimulation by tickling the skin of the side of the trunk causes the hind leg to make scratching movements in the region stimulated (the scratch reflex). Not only this, but other reflexes are also obtainable; thus stimulation of the posterior nerve roots causes, reflexly, a rise of arterial blood pressure. Further study of these reflexes, their characters and their time relations, has proved that reflex movement possesses certain properties which, theoretically, it might be assumed it would possess when the composition of the reflex arc is considered.

These properties are the following:—

1. **The Properties of the Reflex dependent upon the Receptor Nerve Ending.** These are—

(*a*) That any particular reflex response is only obtained in response to a particular variety of stimulus. Thus contraction of the pupil, in response to light, is a reflex phenomenon produced only when the stimulus thrown into the eye is light. Similarly, the passage of a calculus along the bile duct causes a rise of arterial blood pressure, and in this particular instance the dilatation of the bile duct produced by the gall-stone is the only adequate stimulus giving rise to this reflex blood pressure effect. Thus stimulation of the gall-bladder by touching it with the knife (mechanical), or by electrical stimulation, does not produce a rise of blood pressure; although, if the dilatation of the duct, produced by the passage of the gall-stone, is imitated by the injection of fluid into the duct, the characteristic rise of blood pressure is produced. This particular property depends upon the fact that the receptor organ is a definite "sense" organ, differentiated for one particular variety of stimulus.

(*b*) The presence of the receptor organ on the reflex arc lowers the threshold value of stimulation. This means that, in order to produce any particular degree of reflex response, the stimulus, applied to the receptor organ, may be of less intensity than the stimulus applied to the nerve fibre leading from the receptor organ to the efferent arc. This follows naturally from the function of the receptor organ. It is a receptor, or "special sense," organ for particular varieties of stimuli (heat, cold, electrical, mechanical, light, sound, etc.).

2. **Properties dependent upon the Arc of Conduction**—

(*A*) *The Phenomenon of Latent Period.*—By latent period is meant that a certain interval of time elapses between the application of the stimulus to the receptor organ and the appearance of the response in the effector organ. The time is taken up in the following manner:—

1. Latent time in the receptor organ.
2. Time of conduction of the impulse along the afferent and efferent neurones.

3. Time of conduction across the synapses between these neurones.

4. Latent time taken up at the effector organ before the nervous impulse produces a response in it.

With a very strong stimulus applied to the receptor organ, the latent period just corresponds with the first, second, and fourth of these conditions, as determined by calculation, and conduction across the synapses becomes almost instantaneous. If, however, the stimulus is diminished in intensity, then the latent period of the reflex is very distinctly increased, and this can only be due to very much increased delay at the synapses under this condition. Sherrington says that the great increase in the latent period of the reflex with diminution in intensity of stimulation is a more marked feature in spinal reflexes than the actual length of the latent period. With diminution in intensity of stimulus the time taken up in conduction across the synapse is definitely increased.

(*B*) *The Fact that Reflexes are irreversible.*—Conduction takes place in the reflex arc from afferent to efferent neurone, and not in the reverse direction.

3. Properties dependent upon the Synapse—

(*a*) To a great extent reflexes depend upon the condition of the animal. Thus reflexes are very quickly abolished in the asphyxiated animal. This probably depends upon the greater delicacy of the synapse as compared with the nerve fibre.

(*b*) *Reflexes are very readily fatiguable.*—Nerve fibres, as has been shown by Halliburton, and also by Waller, are almost non-fatiguable; whereas reflexes are quite easily fatiguable. In all probability the difference is due to the presence of the synapses.

(*c*) The ease with which *certain drugs* induce alterations in the reflex.

(*d*) *The Phenomenon of temporal Summation.*—Weak stimuli may induce no reflex effect, yet that same strength of stimulus, repeated a number of times, may induce a reflex effect. The summation occurs in either the nerve cell of the efferent neurone or the synapses.

(*e*) *The Property of Facilitation*, whereby, after a stimulus has produced a reflex response, a second stimulus produces the same response more quickly, and with a smaller threshold value of stimulation.

(*f*) *Inhibition*, that, during the progress of production of any one reflex, a mild stimulus, applied to the receptor of a second reflex, will not produce a response; that is to say, the second reflex is inhibited. On the other hand, if the first reflex is only produced by a mild stimulus, a very strong stimulus, applied to a second receptor organ, will cause the first reflex to be inhibited, and may lead to the production of the second reflex.

(*g*) The property of *all or nothing* response: although, in some reflexes, the degree of effector organ response is proportional to the degree of stimulation of the receptor organ, yet in others the response of the effector organ is independent of the strength of the stimulus. In this respect it rather resembles the "all or nothing" law, whereby the response to a stimulus is maximal.

4. Property depending upon the Effector Organ.

The only property depending upon this structure is the character of the response obtained. The effector organ may be—

(*a*) *A Voluntary Muscle*, in which reflex conduction produces either contraction or inhibition.

(*b*) *Cardiac Muscle*, where the reflex response is either acceleration or inhibition of the rate of beat.

(*c*) *Blood Vessels*, where the response is either constriction or dilatation; and,

(*d*) *Glands*, whereby secretion may be excited or inhibited.

V. Property depending upon the whole Reflex Arc.

This property is the property of "fatality,"—that is to say, that a particular stimulus, applied to a particular receptor organ, gives rise to one kind of response only; the only changes manifested are those in quantity, never in quality.

THE RECIPROCAL INNERVATION OF ANTAGONISTIC MUSCLES (SHERRINGTON).

This furnishes one of the best examples of nervous co-ordination that exists in the body. The reciprocal innervation of antagonistic muscles will be readily understood from the following considerations.

A mechanical stimulus (*e.g.* a blow) applied to the tendon of the quadriceps extensor cruris causes extension at the knee, produced by contraction of the quadriceps extensor muscles. Now, every joint is supplied by two groups of muscles, namely, *Flexors* and *Extensors.*

It is obvious that these different groups of muscles have opposite actions, and that contraction of one group, provided that the other group remains in its ordinary condition, will cause stretching of the opposing group. Such an arrangement as this tends to cause delay in the execution of any particular movement. On the other hand, if contraction of one group of muscles is accompanied by relaxation of the antagonistic muscles, a perfectly balanced and smooth action must be obtained; such an action occurs in response to stimulation of the quadriceps extensor tendon. The knee-jerk is caused by contraction of the quadriceps extensor muscle, but this contraction is accompanied by simultaneous relaxation of the hamstring muscles which normally tend to prevent the extension.

This statement is proved by the following observations:—

1. If the flexor muscles are examined during the production of a knee-jerk, they are found to become softer.

2. If in an animal the tendons of the hamstrings are detached from the tibia, and connected with a recording apparatus, the muscles are found to elongate during the production of the knee-jerk.

3. Further, this inhibition of the flexors is of reflex origin, because, if the nerves to the flexor muscles are divided and the knee-jerk elicited, the inhibition is not obtained.

The inhibition of the flexors might be produced in one of two ways:—

(*A*) *As the result of a Reflex*, the afferent nervous arc of which passes from the extensor muscles to the cord, the efferent arc from the cord to the flexor muscles.

There is experimental support for this view of the following nature:—

1. One-third of all nerves connected with muscles consists of afferent nerve fibres; these nerve fibres originate in the neuro-muscle spindles, and in the tendon organs of Golgi present in the muscle and the tendon respectively.

2. Stimulation of the central cut end of the nerve to the

hamstrings causes inhibition and elongation of the extensor muscles.

3. Stimulation of the end organs, by stretching the hamstring muscles, causes elongation and inhibition of the extensor muscles, together with inhibition of the knee-jerk.

(*B*) *The second Method of producing Inhibition of an Antagonist Muscle.*—Stimulation of the neuro-muscle spindles in that muscle by mechanical stimulation, such as stretching; this muscle spindle stimulation causes reflex inhibition. In this case the afferent nerve fibre comes from the muscle itself and not from its antagonist. Probably both of these mechanisms are brought into play in the production of the reflex inhibition of the hamstrings during the "knee-jerk" contraction of the extensors.

Similarly, during the movement of any joint, whether by reflex or voluntary means, there will be contraction of one group of muscles, and relaxation of the antagonistic group. Probably in the case of voluntary movements the inhibition may be of central origin, since Sherrington seems to have demonstrated the presence of inhibitory impulses descending in the lateral column of the spinal cord; but at the same time it requires for its proper co-ordination afferent impulses from the muscles themselves, and if these are cut out, as occurs in locomotor ataxia, there is loss of reflexes, and consequently a loss of muscular co-ordination.

REFLEXES WHICH OCCUR IN THE HUMAN BODY.

In the human body a number of reflexes may be obtained, which are of great importance because they are the clinical indicators of the state of the nervous system. Alterations in the normal condition of the nervous system lead to alteration in the reflexes elicitable through it.

Reflexes in man are usually divided into three groups—

(1) The superficial reflexes, which are true reflexes.

(2) The deep reflexes, which include the tendon reflexes. Although the tendon reflexes depend upon the integrity of the reflex arc (*i.e.* afferent and efferent neurones) in connection with the tendon and muscle activated, they are not themselves true reflexes.

(3) Visceral or organic reflexes.

I. The Superficial Reflexes (*vide* p. 516).

1. The Eye Reflexes.

(*a*) Stimulation of the cornea causes closure of the eyelids—the conjunctival reflex.

(*b*) Allowing bright light rays to fall upon the retina causes contraction of the pupil—the direct light reflex (*vide* p. 647).

(*c*) Light rays stimulating the retina of one eye cause contraction of the pupil of the other eye—the consensual light reflex (*vide* p. 648).

(*d*) Painful stimulation of the skin of the neck causes dilatation of the pupil of that side (*vide* p. 649).

2. Plantar Reflexes.

(*a*) Tickling the soles of the feet causes their withdrawal.

(*b*) Stroking the sole of the foot causes plantar flexion of the toes (flexor response).

3. **Abdominal Reflexes.**—Stimulation of the skin of the abdomen causes contraction of the underlying muscles. There are two types of this reflex—

(*a*) The upper, in which the skin over the epigastric region is stimulated—the upper or epigastric reflex; and,

(*b*) The lower abdominal reflex, in which the skin over the lower part of the abdomen is stimulated—the hypogastric reflex.

4. **Gluteal Reflex.**—Stimulation of the skin over the buttock causes contraction of the underlying gluteus maximus (*vide* p. 516).

5. **The Cremasteric Reflex.**—Stimulation of the skin at the inner side of the thigh causes retraction of the testis on the side stimulated.

Other important examples of superficial reflexes are—

(1) The inspiratory gasp and temporary cardiac inhibition following the application of cold water to the skin (*e.g.* the cold bath).

(2) The dilatation of the peripheral arterioles, and the cardiac acceleration produced by the application of warmth to the body.

II. The Deep Reflexes (*vide* p. 517).

Examples of tendon reflexes, which are sometimes called deep reflexes, are to be found in the ligamentum patellæ, the tendo Achillis, the supinator longus, the biceps cubiti, and the triceps reflexes, and the phenomenon of ankle clonus. All these reflexes resemble one another in the conditions which determine their production. These are—

1. The muscle connected with the particular tendon is, to a slight degree, put upon the stretch.

2. The tendon is then tapped sharply, so that its tension is suddenly increased; and,

3. The response is a sudden contraction of the muscle connected with the tapped tendon.

1. **The Knee-Jerk.**—This is elicited by tapping the tendon of the quadriceps extensor of the knee (which has been previously put on the stretch by flexing the leg), when the response shows itself as a kick forward of the leg and foot, due to contraction of the quadriceps extensor cruris. For a long time it was thought that this was a true reflex; but Waller and others showed conclusively that this could not be the case, because the latent period of response (the time elapsing between stimulation and response) is much too short to allow of nervous conduction from the point stimulated up to the cord and back again to the extensor muscles. It, however, depends upon the reflex arc of the extensor muscles (especially the vastus internus) being intact. The knee-jerk depends upon the tonicity of the extensor muscles; if the tonicity of these muscles is small, then the knee-jerk is only obtained with difficulty, whilst if the tonicity of the muscles is definite, the knee-jerk is brisk; the tonicity of these muscles depends upon the integrity of the reflex arc connecting them with the central nervous system. So that, although the knee-jerk itself is not a reflex, yet it depends upon a reflex. The knee-jerk itself is simply the response of muscles to a mechanical stimulation.

2. Similarly the **biceps, triceps, supinator longus, and tendo Achillis jerks** are obtained by placing their corresponding muscles upon the stretch, and applying a sharp tap to the tendon by means of an appropriate instrument.

3. **The Ankle Clonus.**—This reflex is one which, as a rule, is absent in health. In those people in whom it is present it is obtained by bringing the foot quickly towards the anterior aspect of the tibia by sharp pressure applied to the sole. The soleus muscle of the calf contracts as a result of the strain to which the tendo Achillis is subjected, and if the

pressure is continued the contraction becomes clonic, *i.e.* repeated at short intervals.

III. The Visceral or Organic Reflexes.

1. **Deglutition.**—Deglutition is a reflex, the motor response showing itself in peristaltic contraction of the œsophagus, and dilatation of the cardiac orifice of the stomach, resulting from stimuli applied behind the anterior pillar of the fauces.

2. The processes of micturition and defæcation (*vide* pp. 446, 165).

3. The rise of arterial blood pressure produced reflexly by the passage of a gall-stone along the bile duct (*vide* p. 491).

4. The dilatation of the splanchnic arterioles which occurs reflexly as a result of increased tension in the left ventricle and in the first part of the aorta (*vide* p. 217).

5. The normal mechanism of respiration (p. 324).

6. The constriction (or dilatation) of the cutaneous arterioles produced reflexly by vaso-dilatation (or constriction) of the vessels of the splanchnic area.

The Principles of the Final Common Path.

The muscles of the body have one nerve supplying them, or possibly two—one motor and the other inhibitory, and all stimuli passing to the muscle must pass along these nerves. That is to say, that no matter where any given nervous impulse is generated, that nervous impulse to reach the muscles must pass along that nerve; in other words, the motor nerve is the public path, or the final common path, to the muscles.

On the other hand, the nervous impulse passing to the muscle may be generated over a very wide area of the body, and may originate in very widely separate afferent arcs. It is obvious that from any one spot on the skin there is only one afferent nerve, so therefore these must be considered as private paths.

To give an example—

Activation of the hamstring muscles of the "spinal dog's" leg may be produced by any one of the following methods:—

1. Stimulation of the sole of the foot, which causes con-

traction of the flexor muscles, and withdrawal of the foot from the zone of stimulation.

2. Stimulation by the faradic current of a large saddle-shaped area of skin on the side of the animal results in the scratch reflex, rhythmical successive movements of flexion and extension.

3. Stimulation of the afferent fibres from the extensor muscles to the cord causes reflex inhibition of the flexor muscles of the knee.

Now, it will be noticed that all the nerve stimuli have to ultimately find their way to the flexor muscles along one nerve,—the motor nerve to the flexor muscles. That is to say, all the nerve impulses which traverse the private paths provided by the afferent nerves from the sole of the foot, the intercostal nerves from the sides of the flank, and the afferent nerve from the extensor muscle, had to ultimately traverse the public or final common path afforded by the motor nerve to the flexor muscles.

Upon the nerves to the flexor muscles there converge, therefore, a very wide series of afferent arcs, and there is consequently the possibility of the production of an indefinite number of reflexes, and the important question hence arises, as to what particular reflex will be elicited when two or more of the afferent arcs are simultaneously stimulated.

An experiment bearing upon this subject has been performed by Sherrington. In a "spinal dog" he elicited the scratch reflex, and during the progress of this reflex (without stopping the faradic stimulus which was producing the scratch reflex) he stimulated the sole of the same foot. The result was that the scratch reflex ceased, the foot was flexed and drawn up, but directly the stimulus eliciting this latter ceased, the scratch reflex returned.

The following appear to be the chief factors which determine which of two or more reflexes should proceed :—

1. The character of the stimulus producing the reflex. If the stimulus is painful, or of a character likely to do damage to the animal, then the reflex corresponding with this stimulus results.

2. The strength of the stimulus. The stronger the stimulus the greater likelihood there is of the corresponding response resulting.

3. If one reflex has already been fatigued, then a second may be elicited.

Irradiation of the Reflexes.

If a sensory stimulus is applied to any part, a reflex is produced. Further, under ordinary conditions that reflex tends to activate the muscles of the part stimulated, and in fact the muscles particularly affected are those supplied by the same segment of the cord to which the afferent nerve belongs. If, however, the stimulus is greatly increased in intensity, the reflex response is greatly increased too, and thus a nervous impulse passing along the private afferent path then activates a wide area of private motor paths. This spread of response is called *irradiation.* It occurs when the strength of the stimulus is greatly increased, or when a stimulus is greatly prolonged. It occurs when the animal is under the influence of certain drugs (strychnine), even though the strength of the stimulus is not increased. Strychnine, it is interesting to note, has two actions upon the central nervous system—

1. It reduces the resistance to the "forward conduction" of nervous impulses, so that reflexes are very easily produced, and

2. It converts inhibitory impulses into motor, so that the greater number of the reflexes which involve antagonistic muscles are produced, but in an inco-ordinate manner.

An example of irradiation is furnished by the following experiment. If the fore-limb of a "spinal" animal is stimulated, response is obtained (1) in that limb; if the strength of the stimulus is increased, or prolonged, movement is obtained (2) in the hind-limb of the same side; and, if the stimulus is continued, the march of the reaction is as follows:—

3. Movement of the tail.
4. Movement of the contra-lateral hind-limb.
5. Movement of the contra-lateral fore-limb.

Similarly, the march of reaction, when a hind-limb is stimulated, is as follows:—

1. Contraction of the hind-limb.
2. Movement of the tail.
3. Movement of the homonymous hind-limb.
4. Movement of the contra-lateral fore-limb.

Or when the pinna is stimulated—

1. Movement of neck away from side stimulated.
2. Movement of homonymous fore-limb.
3. Movement of homonymous hind-limb.
4. Movement of tail.
5. Movement of contra-lateral hind-limb.
6. Movement of contra-lateral fore-limb.

CHAPTER XXXVIII.

THE SPINAL CORD.

In the spinal cord the nerve fibres, which belong to the neurones, and which convey the afferent and efferent nerve impulses, are present in the outer portion, and constitute the white matter of the cord. The more centrally placed grey matter chiefly consists of nerve cells and their processes; this portion of the spinal cord is well supplied with blood vessels through the pia mater which surrounds the cord. In the middle of the spinal cord is the central canal, which contains cerebro-spinal fluid. This canal is lined by a columnar ciliated epithelium, which is surrounded by neuroglial tissue called the substantia gelatinosa centralis. Neuroglia is also present at the surface of the cord, and around the apex of the posterior horn.

THE WHITE MATTER OF THE SPINAL CORD.

The white matter of the spinal cord may be conveniently subdivided into tracts, of which some undergo ascending degeneration, others undergo descending degeneration, and those which contain association fibres, of which some undergo an ascending and others a descending degeneration.

Tracts which undergo an Ascending Degeneration.

1. Postero-median column of Goll.
2. Postero-external column of Burdach.
3. Direct or dorsal cerebellar tract of Flechsig.
4. Ascending antero-lateral or ventral cerebellar tract of Gowers.
5. Marginal bundle of Lissauer.

Tracts which undergo a Descending Degeneration.

1. Crossed pyramidal tract of Türck.
2. Direct pyramidal tract of Türck.

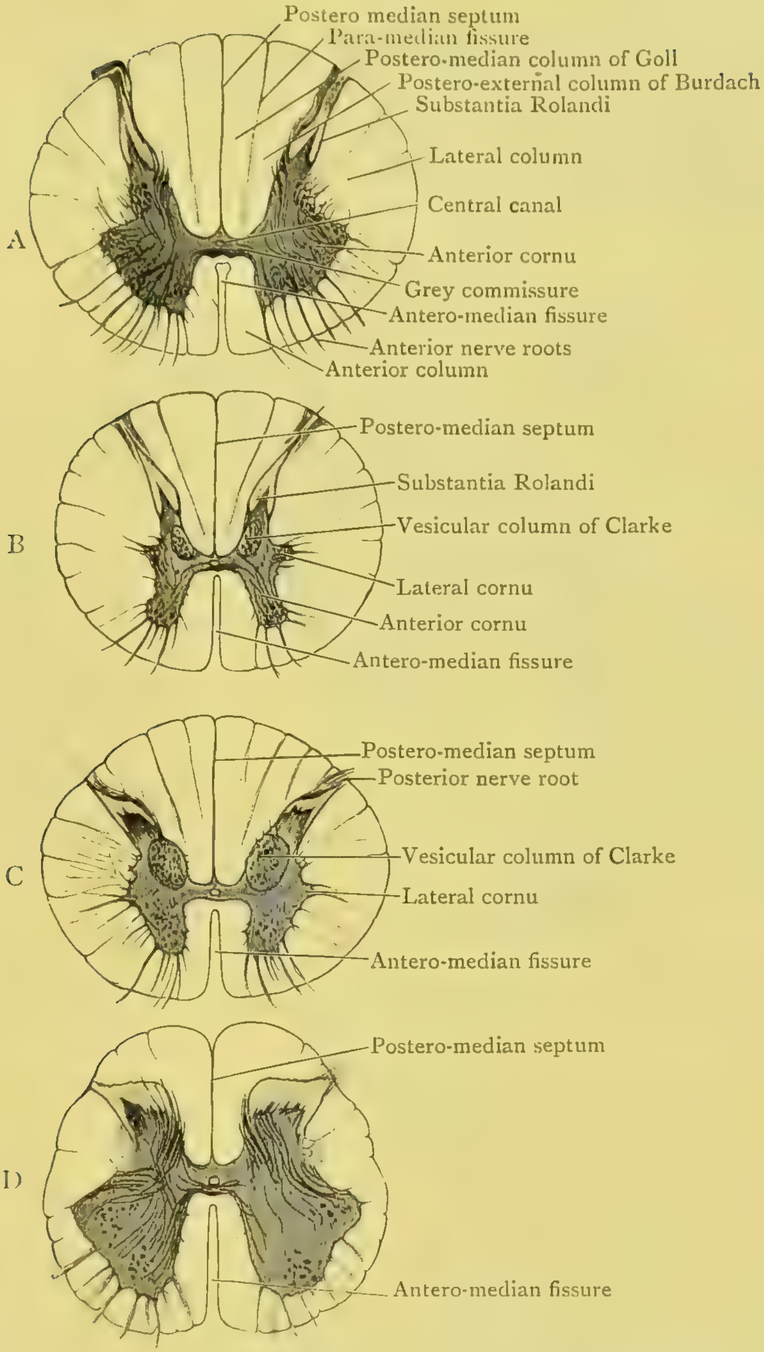


FIG. 66.—Transverse sections of the spinal cord.
(*After* Cunningham.)

A = Cervical region.
B = Mid-dorsal region.
C = Lower dorsal region.
D = Lumbar region.

3. Antero-lateral descending tract of Löwenthal.
4. Pre-pyramidal or rubro-spinal tract of Monakow.
5. Bundle of Helweg.
6. Descending comma tract of Nansen.
7. Median triangular bundle.
8. Median oval bundle.

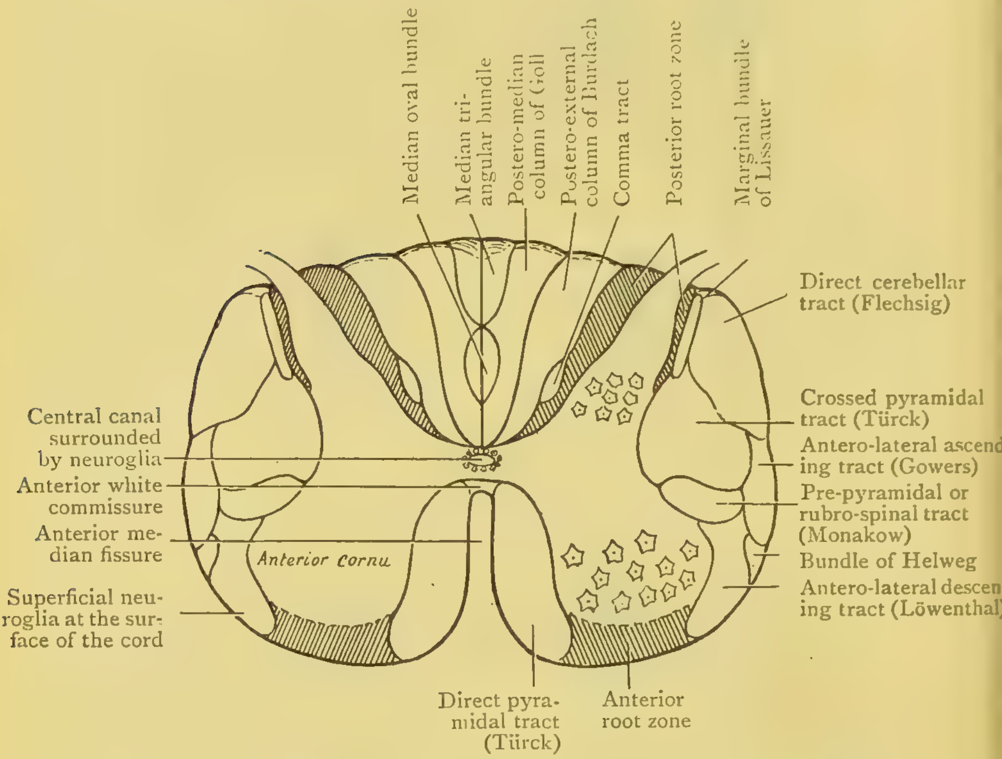

Median oval bundle
Median tri-angular bundle
Postero-median column of Goll
Postero-external column of Burdach
Comma tract
Posterior root zone
Marginal bundle of Lissauer
Direct cerebellar tract (Flechsig)
Crossed pyramidal tract (Türck)
Antero-lateral ascend ing tract (Gowers)
Pre-pyramidal or rubro-spinal tract (Monakow)
Bundle of Helweg
Antero-lateral descen ing tract (Löwenthal
Central canal surrounded by neuroglia
Anterior white commissure
Anterior median fissure
Superficial neuroglia at the surface of the cord
Anterior Cornu
Direct pyramidal tract (Türck)
Anterior root zone

FIG. 67.—Diagram of a transverse section of the spinal cord in the cervical region.

√ The Association Fibres in the Spinal Cord.

According to Sherrington, these intraspinal fibres are scattered in the white matter of the cord, especially in the lateral columns. They are particularly numerous upon the margins of the cord, and some of them undergo an ascending others a descending degeneration. These association fibres serve to convey reflex nerve inpulses *down* as well as *up* the spinal cord.

√ The Ascending Tracts of the Cord.

1. THE POSTERO-MEDIAN COLUMN OF GOLL.—The fibres which traverse this tract are exogenous in origin. They are

derived from the nerve cells present in the posterior nerve root ganglia. These fibres enter the cord by the posterior root zones, traverse the postero-external column of Burdach, and then enter the postero-median column of Goll. The fibres belonging to the postero-median column of Goll, on reaching the medulla, form the funiculus gracilis, and then arborise around the nerve cells which constitute the nucleus gracilis.

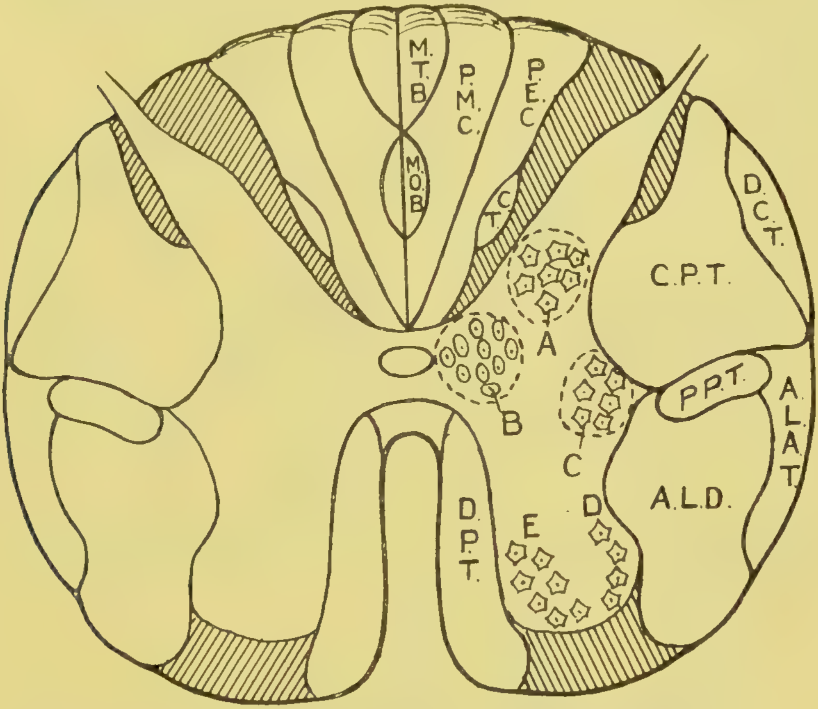


FIG. 68.—Diagram of a transverse section of the spinal cord in the dorsal region.

A = Posterior cornual cells.
B = Cell column of Clarke.
C = Cells in the lateral cornu.
D = Lateral group of anterior cornual cells.
E = Mesial group of anterior cornual cells.

2. THE POSTERO-EXTERNAL COLUMN OF BURDACH.—The fibres in this column are also of exogenous origin. They too are derived from the nerve cells in the posterior nerve root ganglia. They enter the spinal cord by the posterior root zone which is present around the posterior grey cornu, and travel up the spinal cord to the medulla, where they form the funiculus cuneatus. The fibres of this tract arborise around the nerve cells which constitute the nucleus cuneatus.

3. THE MARGINAL BUNDLE OF LISSAUER.—This bundle of fine fibres is present in the lumbar, dorsal, and cervical regions of the cord, and lies just external to the posterior cornu of the grey matter. Its fibres are of exogenous origin, coming into the cord through the posterior root zone, from nerve cells present in the posterior nerve root ganglia. The fibres of this tract appear to pass into the posterior cornu of the cord.

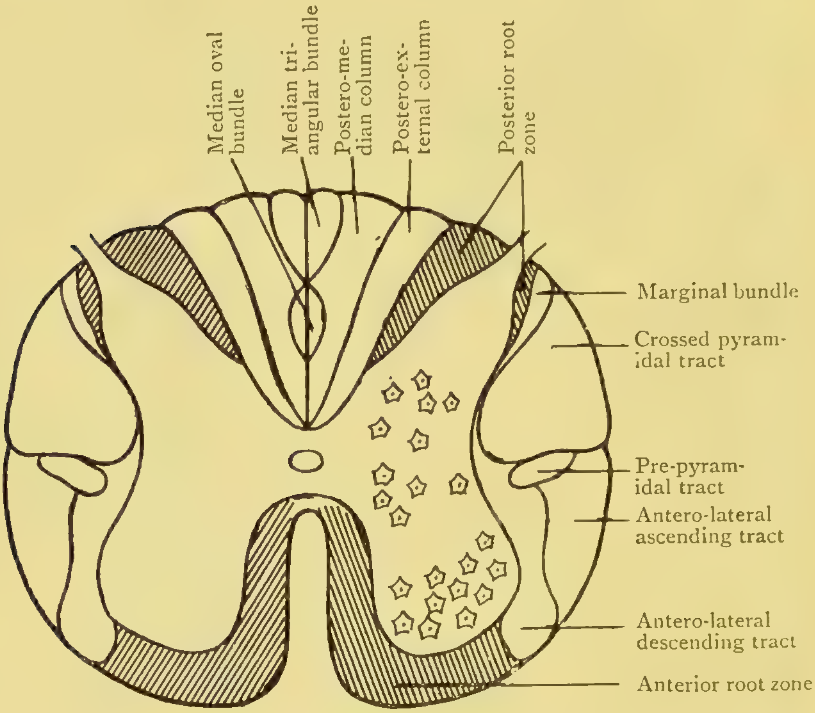


FIG. 69.—Diagram of a transverse section of the spinal cord in the lumbar region.

4. THE DIRECT OR DORSAL CEREBELLAR TRACT OF FLECHSIG (DORSAL SPINO-CEREBELLAR BUNDLE).—The fibres in this tract are endogenous in origin. They are derived from the group of bipolar nerve cells which are present in the lower cervical, dorsal, and upper lumbar region of the cord, and which constitute the vesicular column of Clarke.

The dorsal cerebellar tract is present in the dorsal and cervical regions of the spinal cord. It traverses the medulla in the tract known as the restiform body. The fibres from this tract then travel upwards through the inferior cerebellar peduncle, and eventually arborise around the cells of Purkinje in the vermis of the cerebellum.

5. The Ascending Antero-lateral or Ventral Cerebellar Tract of Gowers (Ventral Spino-cerebellar Bundle).—The fibres in this tract are of endogenous origin, and are derived from the spheroidal-shaped cells which constitute the vesicular column of Clarke of the *opposite* side, and also of the same side of the cord. This tract is present in the lumbar, dorsal, and cervical regions of the cord. The fibres of this tract traverse the medulla oblongata and pons Varolii of the same side, and, having reached the upper part of the pons, make three separate connections. Some of the fibres arborise around cells in the anterior corpus quadrageminum; others traverse the tegmentum of the mid-brain and arborise around the cells in the optic thalamus; whilst a third set of fibres turns back along the superior cerebellar peduncle to arborise around the cells of Purkinje present in the vermis. The tract of Gowers gives off a few fibres, which cross the middle line in the pons, and traverse the middle cerebellar peduncle to enter the opposite half of the cerebellum.

6. The Anterior Sulco-marginal Tract of Marie occurs in man amongst the fibres of the direct pyramidal tract close to the anterior median fissure. Its fibres are of endogenous origin.

The Descending Tracts of the Cord.

1. The Crossed Pyramidal Tract of Türck (Cortico-spinal Tract).—The fibres contained in this tract may be divided into two sets,—the crossed and the uncrossed fibres. The crossed fibres are those which are derived from the large pyramidal cells of Betz, which are situated in the ascending frontal lobe of the opposite side of the brain. These projection fibres cross the middle line at the decussation of the pyramid present in the anterior and inferior portion of the medulla. The uncrossed fibres are the projection fibres of the cells of Betz, which are present in the ascending frontal lobe of the brain on the same side. These fibres travel down through the pons and medulla into the spinal cord of the same side.

Both the crossed and uncrossed fibres of the crossed pyramidal tract enter the grey matter of the cord of the same side in the cervical, dorsal, and lumbar region. These fibres then arborise around nerve cells present at the base of the posterior cornu (posterior cornual cells). These cells give rise to short fibres which travel forward, and arborise around the anterior cornual walls of the same side of the end.

It will be understood, then, that the fibres of the crossed pyramidal tract constitute the projection fibres of the upper motor neurones, and the upper motor neurone is connected with the lower motor neurone or the large anterior cornual cell and its projection fibre, by means of the small association neurone present in the grey matter of the cord.

2. THE DIRECT PYRAMIDAL TRACT OF TÜRCK (CORTICO-SPINAL).—The fibres of this tract constitute the projection fibres of the cells of Betz of the ascending frontal lobe of the same side. They traverse the pyramid of the pons and medulla, and travel down the spinal cord on the same side. They gradually cross, however, to the opposite side of the cord by decussating at the anterior white commissure of the cord. This commissure lies at the bottom of the somewhat wide and well-defined anterior median fissure, between it and the anterior grey commissure. The fibres of the direct pyramidal tract then cross in the anterior white commissure to reach the opposite anterior grey cornu, where the fibres arborise around the anterior cornual cells. The fibres of the direct pyramidal tract begin to cross the cord in the cervical region, continue to cross in the dorsal region until there are none left to cross in the lumbar region; hence the direct pyramidal tract is absent from the lumbar region of the spinal cord. This tract is found present only in the spinal cord of man and of the anthropoid apes. It will thus be seen that there are three sets of pyramidal fibres in the spinal cord:—

(*a*) *The crossed fibres of the crossed pyramidal tract*, which are derived from the opposite Betz cell area, the crossing having occurred at the decussation of the pyramid in the medulla.

(*b*) *The uncrossed fibres of the crossed pyramidal tract*, which are derived from the Betz cell area of the same side. These fibres do not cross the middle line.

(*c*) *The fibres of the direct pyramidal tract*, which are derived from the Betz cell area of the same side, but the crossing of these takes place in the anterior white commissure present in the cervical and dorsal regions of the spinal cord.

3. THE ANTERO-LATERAL DESCENDING TRACT OF L WEN-

THAL.—It is possible that some of the fibres of this tract constitute the vestibulo-spinal fibres, which come through the posterior longitudinal bundle from some of the cells present in the nucleus of Deiters of the same side. These fibres pass into the anterior cornua of the grey matter, and arborise around the anterior cornual cells. It is possible that other fibres of this tract are derived from the cells which constitute the vasomotor centre in the medulla, fibres which traverse the cervical region of the cord and pass into the dorsal region, where they arborise around the cells which constitute the lateral horn characteristic of this region of the cord. The cells of the lateral horn give rise to fibres, which for the most part pass directly out of the cord in the anterior roots. These probably furnish outgoing visceral as well as vasomotor fibres.

4. THE PRE-PYRAMIDAL OR RUBRO-SPINAL TRACT OF MONAKOW.—The fibres contained in this tract originate in nerve cells present in the red nucleus contained in the mid-brain of the opposite side. The fibres cross the median raphé in Forel's decussation in the mid-brain, and travel down through the pons and medulla to reach the pre-pyramidal tract of the opposite side. They arborise around the multipolar nerve cells of the anterior grey cornua.

5. THE BUNDLE OF HELWEG (OLIVO-SPINAL TRACT).—The fibres which constitute this bundle arise in some of the nerve cells present in the olivary body of the same side. They gradually disappear in the cervical region of the spinal cord; their destination is unknown.

6. THE DESCENDING COMMA TRACT OF NANSEN.—The fibres in this tract are of exogenous origin, their trophic cells being contained in the posterior nerve root ganglia. They are, in all probability, *descending* collateral branches from some of those fibres present in the posterior root zone, which eventually pass up the cord in the columns of Burdach and Goll. Those fibres pursue a downward course to arborise around the nerve cells which are present at the base of the posterior cornua. These posterior cornual cells are present at a lower level in the cord from that at which the fibres enter.

7, 8. THE MEDIAN TRIANGULAR BUNDLE AND THE MEDIAN OVAL BUNDLE contain the septo-marginal fibres, which are short longitudinal association tracts. The fibres of these tracts are endogenous in origin, and are derived from cells in the grey matter of the spinal cord.

THE GREY MATTER OF THE SPINAL CORD.

In the middle of the grey matter of the cord is the central canal lined by columnar ciliated epithelial cells. External to these cells is a collection of neuroglial cells constituting the substantia gelatinosa centralis. Around the head of each posterior cornu is another collection of neuroglial cells, which constitute the substantia gelatinosa of Rolando, which was originally developed from the substantia gelatinosa centralis.

The grey matter contains nerve cells, some of which are scattered irregularly, others are collected into definite groups. These groups of nerve cells are most defined in the dorsal region of the spinal cord. In this region four definite groups of nerve cells on each side of the cord are described :—

(*a*) The Posterior Cornual Cells.—This group consists of small multipolar nerve cells present at the base of the posterior cornu. They form synapses with nerve fibres which enter the cord by the posterior cornu from the posterior nerve root ganglion, with fibres which enter the grey matter from the crossed pyramidal tract, and also with fibres which enter the grey matter from the descending comma tract of Nansen. The posterior cornual cells give rise to fibres, some of which pass to arborise around the anterior cornual cells of the same side, thus constituting the short association neurones. Other fibres from these cells cross in the posterior grey commissure of the cord to arborise around the opposite anterior cornual cells. Again, other fibres travel to, and arborise around, the cells present in Clarke's column of the same side.

(*b*) The Vesicular Column of Lockhart Clarke.—This column of cells extends in the cord from the level of the seventh cervical nerve to that of the third lumbar nerve. It tapers above and below, and is most defined in the dorsal region. The cells in this column are bipolar,—the shorter pole being below and the longer above. In transverse section these cells appear to be rounded. They form synapses with fibres from the posterior cornual cells, and give rise to the endogenous fibres which travel up the cord in the ipso-lateral dorsal and both ventral cerebellar tracts.

(*c*) The Intermedio-lateral Group of Nerve Cells constitutes the lateral horn which is characteristic of the dorsal region of the spinal cord. These cells form synapses with fibres, which enter this portion of the grey matter from the antero-lateral descending tract. The cells of this lateral horn give rise to fibres, which pass out of the cord through the anterior grey horn, and emerge from the cord with the anterior nerve roots. In all probability these cells constitute the cell stations upon the vaso-motor tract, and act as the subsidiary vaso-motor centres which are present in the dorsal region of the spinal cord.

These small multipolar nerve cells also give rise to fibres which acquire a fine medullary sheath in the anterior root zone, and a primitive sheath in the anterior nerve root. These finely medullated nerve fibres leave the nerve, forming the white rami communicantes or preganglionic fibres, and then enter a neighbouring sympathetic ganglion.

(*d*) THE ANTERIOR CORNUAL CELLS.—These cells are arranged in two groups, the mesial and lateral groups. They are multipolar nerve cells, some of which are larger than others.

The anterior cornual cells form synapses with fibres from the following regions :—

(i) *The posterior cornual cells of the same side.*—This synapse is connected with the direct reflex arc.

(ii) *The posterior cornual cells of the opposite side.*—The fibres cross at the posterior grey commissure. This synapse is connected with the crossed reflex arc.

(iii) *The posterior cornual cells of the same side*, which are connected with fibres from the crossed pyramidal tract.

(iv) *From the direct pyramidal tract of the opposite side.*—The fibres decussate in the anterior white commissure of the cord.

(v) *From the pre-pyramidal or rubro-spinal tract of the same side.*

(vi) *From the antero-lateral descending tract*, which contains the vestibulo-spinal fibres.

The large anterior cornual cells give rise to fibres which traverse the anterior root zone, and there acquire a medullary sheath. They then leave the cord in the anterior nerve roots, and acquire a primitive sheath. These large multipolar nerve cells and their projection fibres constitute the lower motor neurones.

The grey matter of the cord contains finely medullated nerve fibres, some of which cross the middle line in the anterior and posterior grey commissures, and form synapses with the nerve cells present. The grey matter is much more vascular than the white matter. The blood vessels are derived from the pia mater which surrounds the cord, but the largest blood supply is derived from the blood vessels which are present in that portion of the pia mater which is known as the linea splendens, and which dips down into the anterior median fissure of the cord. These vessels are especially distributed to the anterior cornua of the cord, and it is some of these vessels in the grey matter which are found to be thrombosed in the disease known as acute anterio-polio-myelitis, or infantile paralysis.

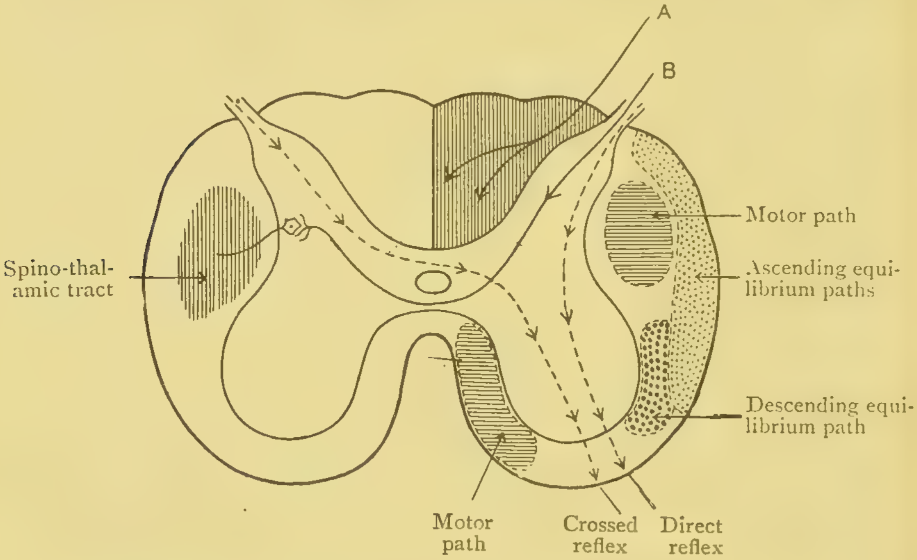


FIG. 70.—Diagram of a transverse section of the spinal cord.

A = { Kinæsthetic sensations.
Uncrossed tactile impulses (a few),—the finer.
Vibration sense (bone sense).

B = { Crossed tactile impulses (most),—the coarser.
Temperature impulses (heat and cold).
Pain sensations.

The spinal cord may be considered from a physiological point of view, as Fig. 70 will serve to show.

Sensations.

From the periphery two sets of impulses originate, the cutaneous and the deep. These eventually arise in consciousness as sensations. Those impulses which arise in the skin and culminate in sensations are broadly referred to as *cutaneous sensations*, and these include sensations of pressure, heat, cold, and pain. They may be subdivided into the coarse or protopathic sensations, and the more accurate or finer or epicritic sensations. These impulses which arise in the deeper structures, such as muscles, tendons, synovial membranes, bone, etc., are referred to as muscle, tendon, synovial membrane, pressure, and vibration sense, and are collectively known as the *deep sensations*. The impulses from these tissues pass up the peripheral sensory nerves, along what is called the peripheral or "primary level," and pass into the spinal cord by the posterior nerve roots. Some of these impulses travel straight into the posterior grey cornua, others pass into the posterior root zone which is present around the posterior grey cornua.

When these afferent impulses reach the spinal cord or the "secondary level," the fibres which convey them become rearranged, so that the afferent impulses from the periphery travel up the spinal cord in different paths.

The "Sensory" Paths of the Cord.

The kinæsthetic sensations which arise in the skin, muscles, tendons, synovial membranes, and ligaments, the finer uncrossed tactile sensations, and the vibration sense derived from bone, pass into the cord at the posterior root zone, and travel up in the postero-external column of Burdach and postero-median column of Goll. For the most part the impulses from the leg pass up the postero-median column of Goll, and those from the arm travel up the postero-external column of Burdach (*vide* pp. 622, 623).

In the disease tabes dorsalis, or locomotor ataxia, the nerve cells of the posterior root ganglia degenerate. This is followed by an ascending degeneration of the postero-external column of Burdach, the postero-median column of Goll, and the marginal tract of Lissauer. The result of these degenerative changes is that kinæsthetic impulses are either imperfectly sensed, or not sensed at all.

The coarser tactile sensations, along with the sensations of heat, cold, and pain, travel into the posterior grey cornua, thence into the central grey matter, crossing the cord at the anterior grey commissure. The fibres which convey these impulses appear to make cell stations at the base of the opposite posterior cornua, and from some of these posterior cornual cells new fibres arise which conduct these impulses up the spinal cord through the spino-thalamic tract. These impulses therefore eventually arrive at the optic thalamus, and by the thalamo-cortical fibres gain the grey matter of the cerebral cortex. The nerve fibres from the spinal cord, which convey the impulses which eventually give rise to sensations of heat, cold, and pain, travel up through the medulla external to the olivary body, and in this region they mix with the fibres coming up from the tract of Gowers. Both these sets of fibres eventually reach the optic thalamus. In the disease syringomyelia, in which there appears to be an overgrowth of the neuroglial tissue of the grey matter of the cord with subsequent degeneration, many of the nerve fibres which convey afferent impulses across the grey matter become involved in the disease. The consequence of this is that the patient ceases to appreciate the impulses of heat, cold, and pain.

The Motor Paths of the Cord.

The efferent or motor paths of the cord lie in the crossed and the direct pyramidal tracts. The motor impulses, which arise in the cortex of the *right* side of the brain, travel down through the corona radiata, through the internal capsule of the corpus striatum, through the central part of the crusta of the crus cerebri, thence through the longitudinal fibres of the pons into the medulla. At the lower part of the medulla these efferent impulses may take one of three courses; they may

(*a*) Travel across the decussation of the pyramid, and thence down the *left* crossed pyramidal tract of the cord. The impulses then travel into the grey matter at the base of the posterior cornua. They then travel forward through the anterior cornual cells to the projection fibres which help to form the anterior nerve roots of the cord (the motor roots); or they may

(*b*) Travel down the direct pyramidal tract of the cord and gradually cross in the cord at the anterior white commissure to gain the opposite anterior grey cornua. The motor impulses then travel out of the cord through the lower motor neurone; or they may

(*c*) Travel down in the uncrossed fibres of the crossed pyramidal tract, through the posterior cornual cells and their short projection fibres, to the lower motor neurones of the same side. These fibres, in all probability, convey motor impulses to the ipso-lateral leg.

It will be seen, therefore, that the right half of the cerebral cortex chiefly controls the opposite half of the body by means of efferent impulses, which travel down the contra-lateral crossed pyramidal tract and the ipso-lateral direct pyramidal tract. At the same time it will be seen that the right half of the cerebral cortex does exercise some control over the right side of the body by means of efferent impulses, which travel down the uncrossed fibres contained in the ipso-lateral crossed pyramidal tract. It will be observed, therefore, that movements performed by both halves of the body are bilaterally represented upon the cerebral cortex. The movements which occur in the arms and legs are unequally bilaterally represented, whereas the movements which occur in the muscles of the thorax and abdomen, that is, in the regions where muscles habitually work together, are equally bilaterally represented (Broadbent's law), and this mechanism is provided for by the uncrossed fibres of the crossed pyramidal tracts. A unilateral lesion of the spinal cord, occurring *below* the cervical enlargement (the arm fibres thereby escaping), produces monoplegia of the leg of the same side, and also some anæsthesia of the opposite leg. Such paralysis of one leg with anæsthesia of the other is known as "Brown-Séquard paralysis."

The Reflex Movements of the Cord.

The reflex movements obtained through the cord may be divided into two sets, the direct and the crossed reflexes. The *direct* reflex movement is brought about by afferent impulses reaching the cord by the posterior nerve roots, entering the posterior grey horn, and travelling across to the anterior grey horn of the same side. The impulses which result in the movement leave the cord by the anterior nerve roots. In the case of the *crossed* reflexes the afferent impulses reach the cord by the posterior nerve roots upon one side, and travel across the grey matter by the posterior grey commissure, and so arrive at the contra-lateral anterior grey horn. Both the direct and crossed reflex movements may be controlled by impulses which descend from the brain; in other words, the brain may exercise an inhibitory influence over the various reflex movements. The reflex movement of insemination, however, cannot be inhibited.

The reflex motor response to a given stimulus, producing an afferent impulse, takes an appreciable time. The delay occurs in the nerve cells at the base of the posterior horn, and in those at the anterior horn through which the impulses travel. This delay may be increased by the administration of drugs, such as chloroform, or it may be diminished by the administration of other drugs, such as strychnine. It has been already stated that the administration of strychnine leads to the rapid spread of reflex movements both up and down the spinal cord (*vide* p. 501).

The reflex movements in man may be divided into the superficial, *e.g.* the plantar reflex, the deep or tendon reflexes, *e.g.* the knee-jerk, and the visceral or organic reflexes, *e.g.* micturition (*vide* p. 445). The following are some of the more important reflexes of the cord (after Purves Stewart):—

SUPERFICIAL REFLEXES.

Reflex.	Method of Eliciting.	Result.	Segmental Level.
Scapular .	Stroking skin of inter-scapular region.	Scapular muscles contract.	C 5 to D 1
Epigastric .	Stroking downwards from nipple.	Epigastrium dimples on side of stimulus.	D 7 to D 9
Abdominal	Stroking downwards from costal margin.	Abdominal muscles contract on side of stimulus.	D 11 to L 1
Cremasteric	Stroking inner and upper part of thigh.	Testicle is pulled up.	L 1 and L 2
Gluteal .	Stroking skin of buttock.	Gluteal muscles contract.	L 4 and L 5
Plantar .	Stroking sole of foot.	Tensor fasciæ femoris contracts, hallux and other toes flex, ankle is dorsi-flexed.	L 5 to S 2

The normal plantar reflex (flexion of the toes) only occurs when the reflex arc is intact, and in connection with the motor portion of the cortex cerebri by fully developed and uninjured pyramidal fibres. If the pyramidal tract is undeveloped (as in infants) or diseased, the plantar reflex is an *extensor* response of the toes (Babinski's sign).

The patellar tendon reflex, or knee-jerk, is a type of a tendon reflex. The knee-jerk has been already discussed (*vide* p. 497), and it has been pointed out that the patellar tendon reflex is *not* a true reflex, but a phenomenon which depends upon a constant "reflex tonus" in the vastus internus muscle, which tonus is dependent upon a reflex arc. If the reflex arc is interrupted the reflex tonus is lost, and the knee-jerk can no longer be obtained.

Deep reflexes may be exaggerated, so that the slightest tap on the tendon results in a very brisk contraction; such a result occurs in strychnine poisoning. If the pyramidal tracts are sclerosed the deep reflexes may be permanently increased. In these circumstances a clonus may be produced. A clonus is a series of rhythmic muscular contractions brought about by a sudden passive stretching of the tendon; the clonus persists as long as the tension of the tendon is maintained. The commonest clinical variety of clonus is ankle clonus, which may be obtained by passively flexing the knee-joint, and suddenly dorsiflexing the ankle by upward pressure applied to the sole of the foot. The ankle clonus is due to the contraction of the soleus muscle.

DEEP REFLEXES.

Reflex.	Method of Eliciting.	Result.	Segmental Level.
Biceps	Tapping biceps tendon.	Biceps contracts.	C 5 and C 6
Supinator longus	Tapping base of styloid process of radius.	Supinator longus contracts.	C 5 and C 6
Triceps	Tapping triceps tendon.	Triceps contracts.	C 7 to D 1
Knee	Tapping patellar tendon.	Vastus internus, etc. contracts.	L 3 and L 4
Ankle	Tapping tendo Achillis.	Calf muscles contract.	S 1 and S 2

In the grey matter of the spinal cord there are important reflex centres, such as—

1. The centres which preside over muscle tone. If these centres are diseased, as occurs in locomotor ataxia (posterior nerve root ganglion cells degenerate) and infantile paralysis (anterior cornual cells degenerate), there is a loss of muscle tone; in other words, certain muscles become hypotonic.

These centres also preside over the reciprocal action of antagonistic muscles (*vide* p. 493).

2. The higher centres for micturition, defæcation, erection of the penis, insemination, and parturition are situated in the grey matter of the lumbar enlargement of the cord. Recently, however, clinical and pathological evidence has been brought forward, by L. R. Müller and others, which shows that the lowest reflex centres for the contraction of the bladder, and of the neighbouring hollow viscera, possessing non-striped muscular walls, are situated extra-spinally in the hypogastric and hæmorrhoidal plexuses of the sympathetic (Purves Stewart).

3. Subsidiary vaso-motor centres are present in the grey matter of the dorsal region of the spinal cord, possibly in the lateral cornua. These subsidiary centres are controlled by the chief vaso-motor centre in the medulla oblongata.

4. Subsidiary sweat centres are also present in the grey matter of the lower cervical and upper lumbar region of the spinal cord. These subsidiary centres are controlled by one situated in the medulla oblongata.

The Equilibrium Paths of the Cord.

These paths may be divided into the ascending and the descending.

The Ascending Equilibrium Path.—The kinæsthetic impressions which arise in the periphery in the skin, muscles, tendons, synovial membranes, and ligaments of the extremities (in man especially from the legs) travel into the cord by way of the posterior nerve roots, enter the posterior grey cornua, and thence pass chiefly by the cells of the vesicular column of Clarke to the dorsal cerebellar tract and the ventral cerebellar tract. The impressions which travel by the dorsal or direct cerebellar tract arrive in the cerebellum by way of the inferior cerebellar peduncle; those which travel by the ventral cerebellar tract arrive at the cerebellum by way of the superior cerebellar peduncle.

The Descending Equilibrium Path. — The cerebellum originates impulses which descend the spinal cord, and in all probability control the motor impulses, which leave the cord by way of the lower motor neurones. These efferent cerebellar impulses probably originate in the cells of Purkinje of the vermis, and travel by way of the corpus dentatum of the cerebellum to the cells of the nucleus of Deiters, and thence down the vestibulo-spinal fibres, which in all probability are contained in the descending antero-lateral tract of the cord. The efferent impulses then pass from this tract directly to the multipolar cells of the lower motor neurones.

The Association Tracts of the Spinal Cord.

These appear to be present in the white matter of the cord, and are especially numerous at the surface of the cord. The association impulses travel up and down the cord, and in all probability some cross to the opposite side by way of short association fibres.

CHAPTER XXXIX.

THE MEDULLA OBLONGATA.

THE afferent and efferent tracts of the spinal cord are all represented in the medulla. For the most part the nerve cells of the medulla are present in groups which form distinct nuclei, some of which are cell stations, and others represent the nuclei of some of the cranial nerves. The following diagrams represent some of the more important tracts of the medulla, the cell stations in the medulla, and their connections (*vide* Figs. 71 and 72).

The Funiculus Gracilis.—The fibres contained in the postero-median column of Goll traverse the funiculus gracilis of the medulla, and finally arborise around the cells which constitute the nucleus gracilis. The nerve cells of the nucleus gracilis give rise to fibres, some of which pass to the ipso-lateral restiform body, and thence, by the inferior cerebellar peduncle, to the vermis of the cerebellum. Other fibres from the cells of the nucleus gracilis travel deeply into the medulla, and cross the median raphé to gain the opposite side; here some of the fibres travel to the ventral aspect of the medulla, and course round anterior to the pyramid and external to the olivary body. These superficial fibres constitute the external arcuate fibres, and eventually arrive at the restiform body, which they traverse in order to reach the inferior cerebellar peduncle, and finally arrive at the vermis of the cerebellum. It will be understood, then, that cells of the nucleus gracilis give rise to fibres which travel to the ipso-lateral and contra-lateral restiform bodies. Most of the fibres from the nucleus gracilis, which cross at the median raphé, remain deep in the medulla, and constitute the internal arcuate fibres. These fibres then turn forwards to form the lemniscus or fillet which travels forward through the pons to the tegmentum of the mesencephalon.

The Funiculus Cuneatus.—The fibres contained in the postero-external column of Burdach traverse the funiculus cuneatus, and arborise around the nerve cells which constitute the nucleus cuneatus. The nerve cells of the nucleus

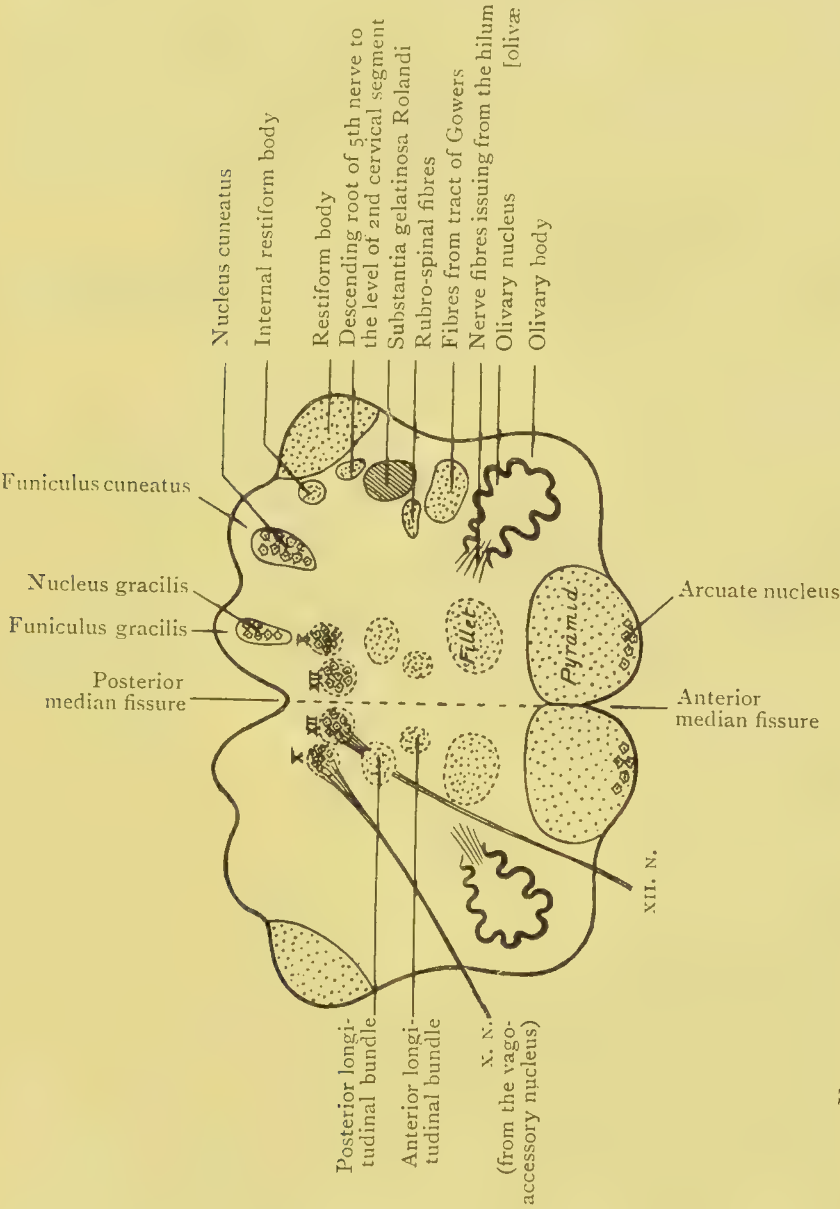

Nucleus cuneatus
Internal restiform body
Restiform body
Descending root of 5th nerve to the level of 2nd cervical segment
Substantia gelatinosa Rolandi
Rubro-spinal fibres
Fibres from tract of Gowers
Nerve fibres issuing from the hilum [olivæ
Olivary nucleus
Olivary body
Funiculus cuneatus
Nucleus gracilis
Funiculus gracilis
Posterior median fissure
Arcuate nucleus
Anterior median fissure
Pyramid
Fillet
XII
XI
X
XII. N.
Posterior longitudinal bundle
Anterior longitudinal bundle
X. N. (from the vago-accessory nucleus)

FIG. 71.—Diagram of a section across the medulla oblongata at the lowest level of the calamus scriptorius.

cuneatus give rise to fibres which make similar connections to those which come from the nucleus gracilis, namely, directly with the ipso-lateral restiform body, with the contralateral restiform body by means of the external arcuate fibres, and with the contra-lateral fillet by the internal arcuate fibres.

The Restiform Body.—The fibres contained in the dorsal cerebellar tract of Flechsig travel up through the medulla in the restiform body, thence by the inferior cerebellar peduncle to the vermis. The restiform body also receives fibres from the nuclei gracilis and cuneatus of the same side, and from the nuclei gracilis and cuneatus of the opposite side, by means of the external arcuate fibres. It also receives fibres from the opposite olivary nucleus by way of the internal arcuate fibres.

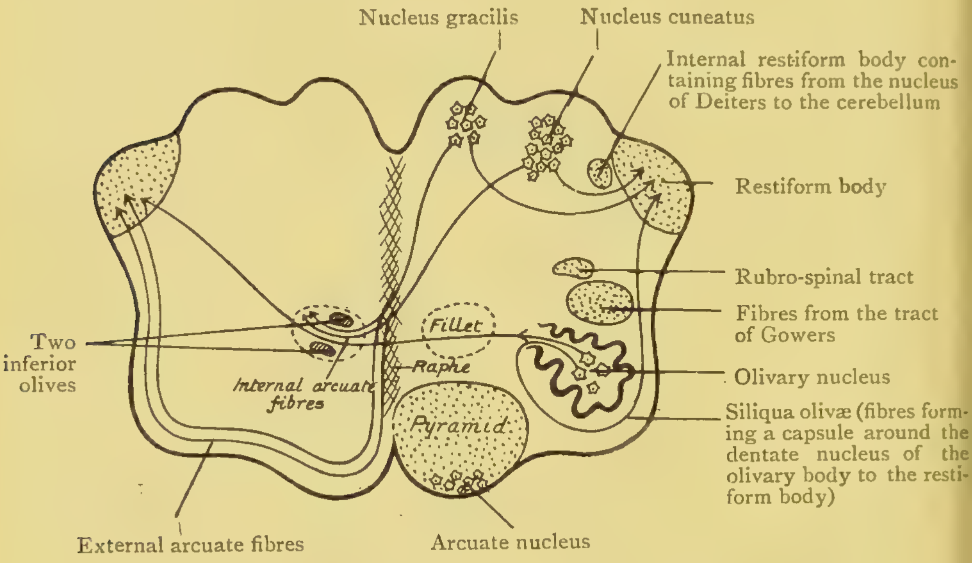

Nucleus gracilis
Nucleus cuneatus
Internal restiform body containing fibres from the nucleus of Deiters to the cerebellum
Restiform body
Rubro-spinal tract
Fibres from the tract of Gowers
Two inferior olives
Fillet
Raphe
Internal arcuate fibres
Olivary nucleus
Pyramid
Siliqua olivæ (fibres forming a capsule around the dentate nucleus of the olivary body to the restiform body)
External arcuate fibres
Arcuate nucleus

FIG. 72.—Diagram to represent the course of the nerve fibres in the medulla.

The Internal Restiform Body.—This lies just internal to the restiform body, and receives fibres from some of the nerve cells contained in the ipso-lateral nucleus of Deiters. These fibres travel to the vermis of the cerebellum. The particular cells of Deiters' nucleus, which give rise to these fibres, receive fibres from the vestibular nucleus, which is connected with the vestibular division of the auditory nerve. In all probability it is in this way that the vestibular impulses from the internal ear make their way to the vermis.

The Tract of Gowers.—The fibres from the ventral cerebellar tract of Gowers traverse the medulla just above the olivary body to reach the pons. The nerve fibres, which carry up the impulses of heat, cold, and pain from the cord, lie just external to the olivary body. They appear to intermingle with the fibres from Gowers tract, and with these traverse the pons and arrive at the optic thalamus.

The Rubro-spinal Tract.—This tract traverses the medulla just dorsal to the fibres from the tract of Gowers. The fibres of this tract come from the nerve cells contained in the contra-lateral red or tegmental nucleus.

The Pyramid.—This lies ventral or anterior in the medulla. The majority of the fibres contained in it come from the Betz cells of the cerebral cortex of the same side. The fibres of the pyramid may take one of three courses down the spinal cord:—

1. In the direct pyramidal tract of the same side; or,
2. In the crossed pyramidal tract of the same side as uncrossed fibres; or
3. Most of the fibres cross at the decussation of the pyramid, which takes place in the anterior part of the medulla, and travel down the cord as the crossed pyramidal tract.

The Olivary Body contains nerve cells which constitute the olivary nucleus. These cells give rise to nerve fibres which leave by the hilum olivæ. A few of these nerve fibres travel ventralwards, turn round the dentate nucleus of the olivary body, forming a capsule to it (siliqua olivæ), and then travel to the ipso-lateral restiform body; thence they traverse the inferior cerebellar peduncle, finally reaching the vermis. Most of the fibres from the dentate nucleus, however, cross the median raphé, get into the bundle composing the internal arcuate fibres, and reach the contra-lateral restiform body, and eventually, through the inferior cerebellar peduncle, reach the vermis of the cerebellum.

The Nuclei of the Cranial Nerves.—The nerve cells, which constitute the nuclei of some of the cranial nerves, lie in the floor of the fourth ventricle on either side of the middle line. The nuclei of the glosso-pharyngeal, spinal accessory (nucleus accessory to the vagus), and the vagus lie in this order from before backwards and external to the nucleus of the hypoglossal nerve. The fibres of the glosso-pharyngeal, spinal accessory, and vagus nerves course ventrally downwards and outwards, leaving the medulla between the olivary body and the restiform body. The hypoglossal nucleus lies near the middle line, and extends throughout the lower two-thirds of the medulla. None of the fibres from the cells of the hypoglossal nucleus cross the middle line, but constitute the hypoglossal nerve, which courses ventralwards and anteriorly to reach the surface of the medulla between the olivary body and the pyramid (*vide* Fig. 73).

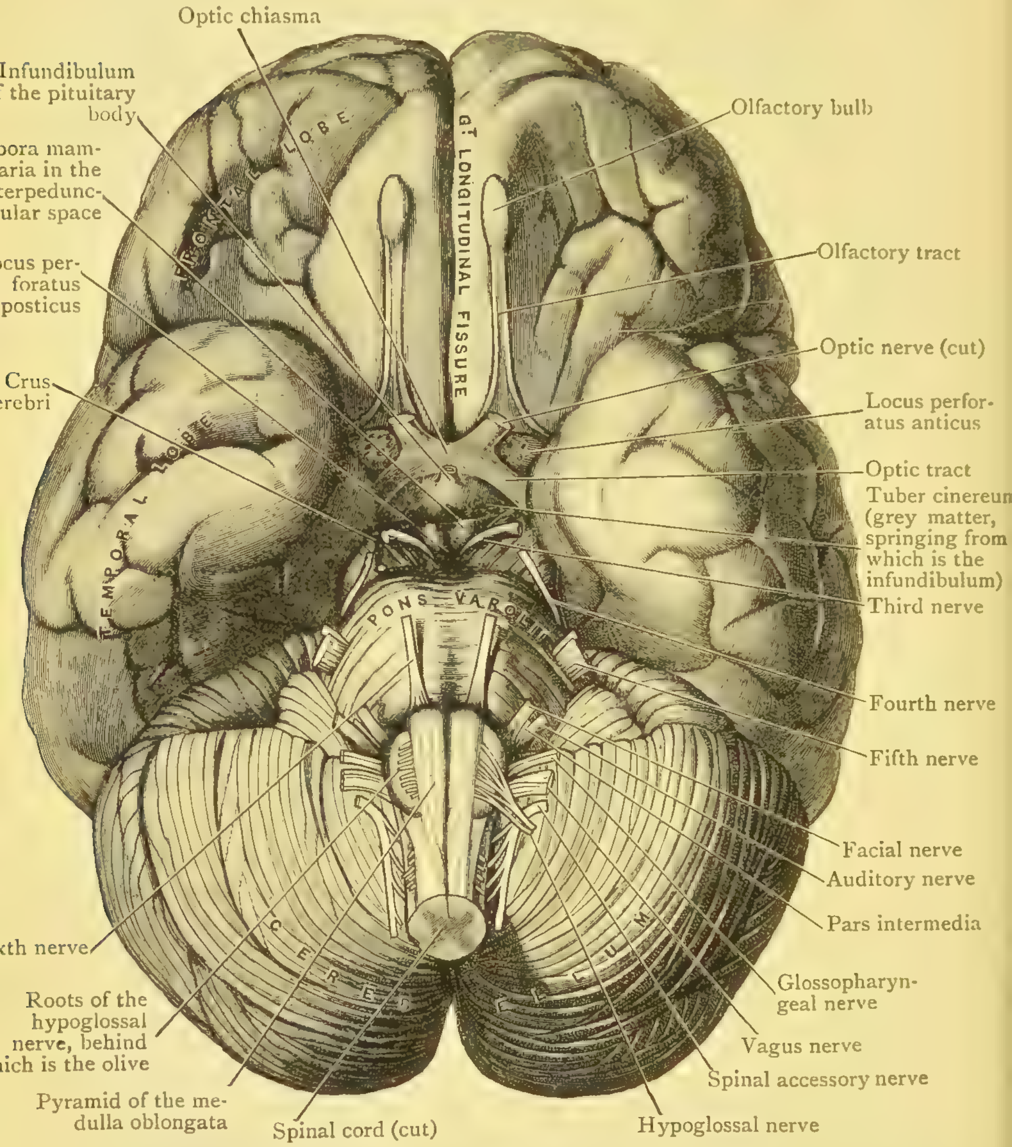


FIG. 73.—The base of the brain with the cranial nerves attached. (Cunningham.)

The Floor of the Fourth Ventricle.—This is formed above by the pons, and below by the medulla; it is covered by columnar ciliated epithelial cells, which below are continuous with the cells lining the central canal of the spinal cord, and above with those lining the iter a tertio ad quartum ventriculum, or the aqueduct of Sylvius, the cells of which are continuous with those of the third ventricle. The columnar ciliated cells lining the third ventricle are also continuous, through the foramina of Munro, with those lining the lateral ventricles. The epithelial cells rest upon, and their prolonged extremities help to form, a layer of tissue called the ependyma of the ventricles of the brain.

The lowest pointed part of the floor of the fourth ventricle forms the *calamus scriptorius.* Here, on either side of the middle line, is the respiratory centre. Just above this is the more extensive vaso-motor centre. In this neighbourhood, on either side of the median furrow of the fourth ventricle, is a cardio-inhibitory centre, and, in all probability, near by is a cardio-accelerator centre. In this region of the floor of the fourth ventricle is the chief sweat centre. Here, too, are the centres for the reflex movements of swallowing and vomiting. This latter is an example of a reflex movement which cannot be inhibited (*vide* p. 155).

CHAPTER XL.

THE PONS VAROLII.

In a transverse section of the pons, tracts of longitudinal fibres and bundles of transverse fibres may be seen, also definite pontine nuclei, and the nuclei of some of the cranial nerves. The following diagram represents some of the structures seen in such a section :—

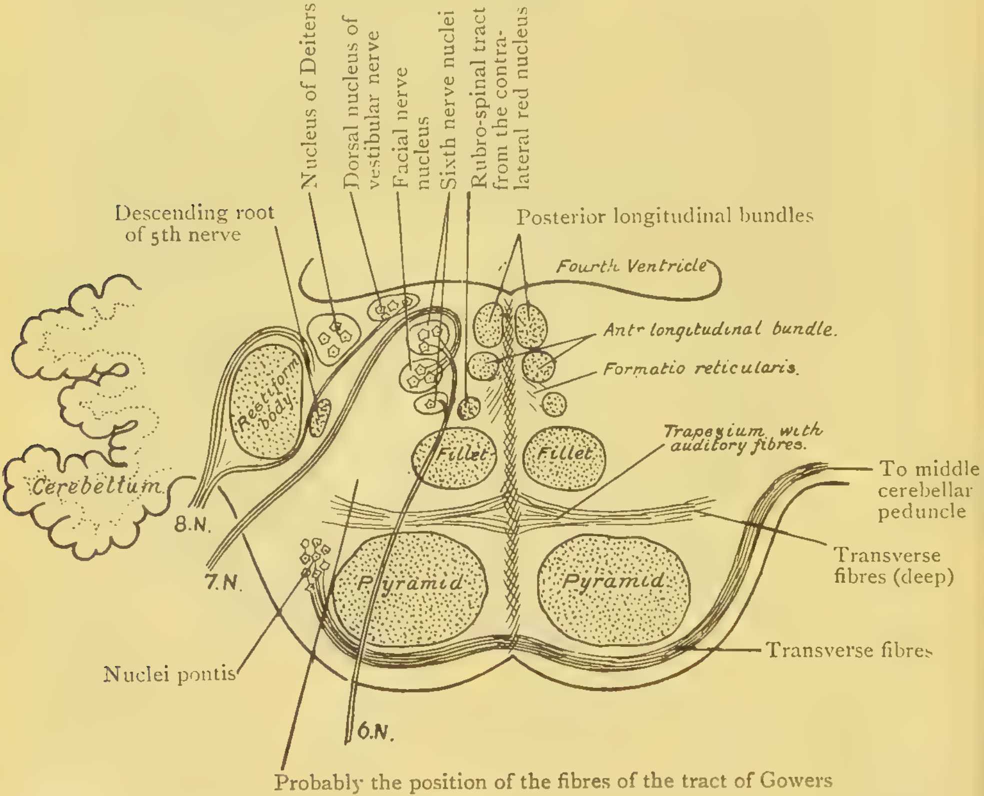

Nucleus of Deiters
Dorsal nucleus of vestibular nerve
Facial nerve nucleus
Sixth nerve nuclei
Rubro-spinal tract from the contra-lateral red nucleus
Descending root of 5th nerve
Posterior longitudinal bundles
Fourth Ventricle
Antr longitudinal bundle.
Formatio reticularis.
Restiform body.
Cerebellum.
Fillet
Fillet
Trapezium with auditory fibres.
To middle cerebellar peduncle
8.N.
7.N.
Pyramid
Pyramid
Transverse fibres (deep)
Transverse fibres
Nuclei pontis
6.N.
Probably the position of the fibres of the tract of Gowers

FIG. 74.—Diagram of a section through the pons Varolii near its lowest portion.

The following diagram represents the connections of the fillet, its fibres being the connecting or intermediate neurones between the spinal afferent neurone and the thalamo-cortical neurones.

The Fillet or Lemniscus.—This commences in the internal arcuate fibres which are present in the medulla, and which lie between the two inferior olives and form the interolivary layer of fibres. The fibres of the fillet traverse the pons near the middle line, being deeply placed, and in the upper part of the pons the fibres of the fillet divide into three sets, forming the mesial fillet, the upper fillet, and the lateral fillet.

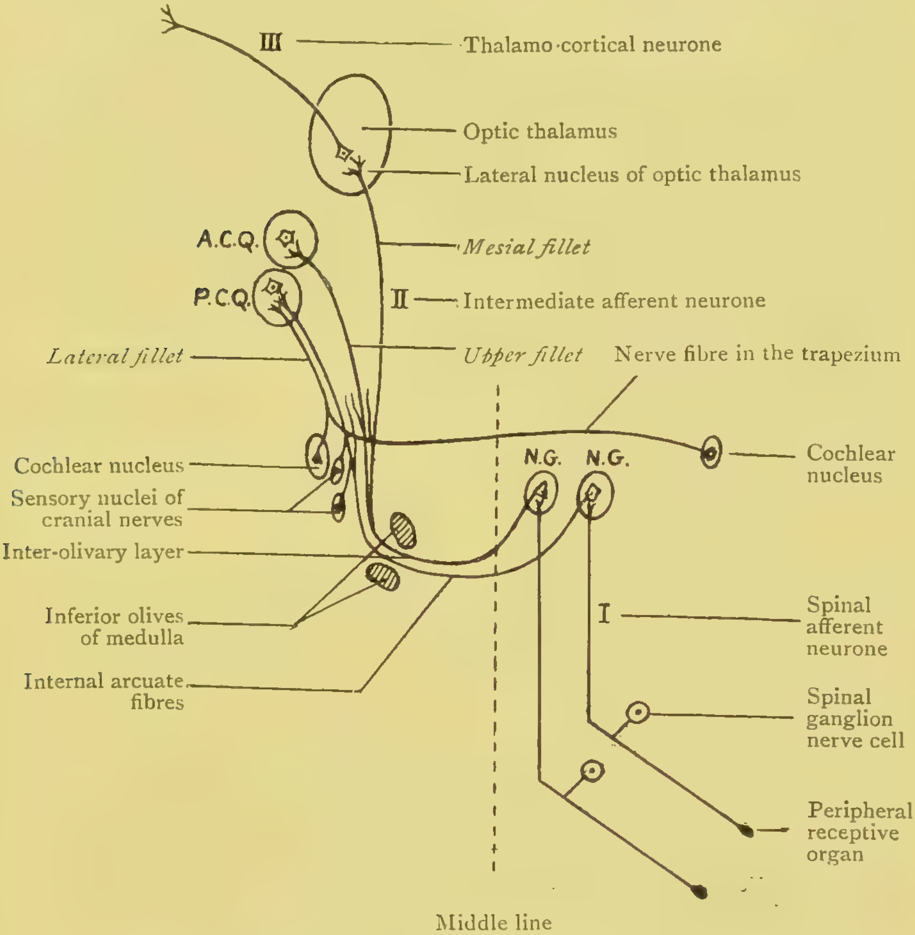


FIG. 75.—The connections of the fillet.

N.G. = Nucleus gracilis.
N.C. = Nucleus cuneatus.
A.G.Q. = Anterior corpus quadrigeminum.
P.C.Q. = Posterior corpus quadrigeminum.

The *mesial fillet* travels forward through the tegmentum of the mesencephalon; and its fibres arborise around cells present in the optic thalamus. The *upper fillet* traverses the tegmentum of the mesencephalon, and its fibres arborise around cells contained in the anterior corpus quadrigeminum. The *lateral fillet* receives fibres from the cochlear nucleus of the same side, and also from the cochlear nucleus of the opposite side. It traverses the outer part of the tegmentum of the mesencephalon, and its fibres arborise around nerve cells in the posterior corpus quadrigeminum.

The afferent impulses, which give rise to kinæsthetic sensations, traverse at least three neurones between the periphery and the cerebral cortex. The lowest or spinal afferent neurone lies between the peripheral receptive organ and the nucleus gracilis or nucleus cuneatus. The second or intermediate afferent neurone lies between the nucleus gracilis, or nucleus cuneatus, and the optic thalamus, and is included in the fillet. The uppermost or third afferent neurone lies between the optic thalamus and the cerebral cortex (thalamo-cortical neurone).

The Restiform Body.—The fibres contained in the restiform body are continued up from the medulla. In the pons some of the fibres of the eighth cranial nerve lie over the dorsal aspect of the restiform body; these are some of the fibres of the cochlear division of the nerve. Other fibres of the eighth nerve, *i.e.* some of the cochlear division and all those of the vestibular division, enter the pons ventral and internal to the restiform body (*vide* Connections of the Eighth Nerve).

The Tract of Gowers.—The fibres from the tract of Gowers ascending the pons reach its upper parts. Most of the fibres which constitute the ventral spino-cerebellar bundle pass back along the superior cerebellar peduncle to the vermis. According to Van Gehuchten, Collier, and Buzzard, the tract of Gowers gives off some fibres to the opposite half of the cerebellum, these reach their destination by way of the middle cerebellar peduncle. Some of the fibres of Gowers' tract reach the anterior corpus quadrigeminum; these constitute the spino-tectal fibres. Other fibres traverse the tegmentum of the subthalamic region and reach the optic thalamus; these constitute the spino-thalamic fibres.

The Pyramids.—These bundles of medullated nerve fibres lie anterior in the pons between the two sets of transverse fibres on either side of the middle line. The pyramidal fibres give off collaterals which arborise around the cells contained in the nuclei pontis of the same side.

The Rubro-spinal Tract.—This tract lies dorsal to the fillet in the formatio reticularis.

The Deep Transverse Fibres.—These fibres form the trapezium which contains commissural fibres between the two sets of auditory nuclei, and also fibres which arise in one set of auditory nuclei which cross to gain the opposite cerebral cortex.

The Nucleus of Deiters.—The cells of this nucleus are large. Its connections are important, and are as follows:—

It receives fibres from the vestibular nucleus of the same side and from the corpus dentatum. The cells composing the nucleus give rise to fibres, some of which pass to the vermis of the cerebellum, others pass out into the posterior longitudinal bundles of *both* sides. In the posterior longitudinal bundles the fibres bifurcate,—one set of branches passes upwards to arborise around cells contained in the sixth and third nerve nuclei, the other set of branches passes down through the medulla and into the spinal cord (probably in the antero-lateral descending tract), constituting the vestibulo-spinal tract. These fibres terminate by arborising around the anterior cornual cells.

The cells in Deiters' nucleus probably constitute a local reflex centre by means of which conjugate movements of the head and eyes are brought about.

The Nuclei Pontis.—These nuclei receive fibres from the frontal lobe of the cerebral cortex of the same side (the cortico-pontine fibres). They also receive many fibres and collaterals from the pyramidal tract. The nuclei pontis give rise to fibres which cross the pons as the superficial transverse fibres, form the middle cerebellar peduncle of the opposite side, and terminate in the vermis. It is through the nuclei pontis that the cerebral hemisphere of one side is connected with the cerebellar cortex of the opposite side.

The Cranial Nerve Nuclei.—The fifth, sixth, seventh, and eighth cranial nerve nuclei are present in the pons. In Fig. 74 of a transverse section of the pons, the descending root of the fifth nerve is seen lying between the restiform body and the fibres of the seventh nerve. In the diagram the two nuclei of the sixth nerve are shown. These nuclei receive fibres which come from the opposite cerebral cortex. The fibres decussate in the pons. The nerve cells of the sixth nerve nuclei not only give rise to fibres which constitute the sixth nerve, but they also give rise to fibres which traverse the posterior longitudinal bundle, and cross to the *opposite* side of the brain to connect with these cells in the opposite third nerve nucleus, which give rise to the nerve fibres supplying the internal rectus muscle. If the sixth nerve nucleus is stimulated by an irritative lesion, such as a hæmorrhage in the pons, the eyes are conjugately deviated to the side of irritation, for the external rectus muscle of the *same* side and the internal rectus muscle of the *opposite* side simultaneously contract and turn the eyes to the side of the irritative lesion.

The seventh nerve nucleus lies between the sixth nerve nuclei. The motor fibres to the stapedius muscle arise from the cells in the mesial portion of the nucleus, then in order come the fibres for the external ear, and then those for the mouth and face. From a group of nerve cells, placed dorsally, the motor fibres arise which are distributed in the temporo-facial branch of the nerve (Marinesco). The nucleus receives motor fibres from the cortex of the opposite side of the brain; these cross to the nucleus of the seventh nerve in the pons. The fibres of the facial nerve course dorsally around the upper nucleus of the sixth nerve, and emerge between the pyramid and the restiform body. It will be seen that a lesion involving the sixth nerve nucleus will most likely implicate the facial nerve fibres, and produce paralysis of the sixth nerve, with resulting internal strabismus *and* facial nerve paralysis on the same side. If the lesion in the pons is more extensive the pyramidal fibres may be involved, with resulting paralysis of the arm and leg of the opposite side. In other words, an extensive lesion in the pons results in a variety of "crossed paralysis," with paralysis of the external rectus muscle of the eye and the muscles of the face on the side of lesion, and paralysis of the arm and leg on the opposite side to the pontine lesion. This condition is known as the "Millard-Gubler syndrome."

CHAPTER XLI.

THE MID-BRAIN OR MESENCEPHALON.

A SECTION across the mid-brain through the posterior corpora quadrigemina goes through the nuclei of the fourth cranial nerves, and also shows the fibres which constitute the lateral fillet containing the auditory fibres. These last-mentioned auditory fibres are distributed to the mesial corpus geniculatum, and also to the nerve cells contained in the posterior corpus quadrigeminum.

The fourth nerve nuclei lie in the grey matter alongside the aqueduct of Sylvius under the posterior corpora quadrigemina. The cells in these nuclei give rise to fibres which travel dorsalwards, and *decussate* above the aqueduct of Sylvius and beneath the posterior corpora quadrigemina, so that the fourth nerve nucleus of the *right* side of the brain gives rise to the fourth nerve fibres of the *left* side. In other words, there is a complete decussation of the fibres of the fourth cranial nerves.

The fillet traverses the tegmentum of the mid-brain in three strands—the *mesial fillet* ending in the optic thalamus, the *upper fillet* reaching the anterior corpus quadrigeminum, and the *lateral fillet* with auditory fibres arriving at the posterior corpus quadrigeminum (*vide* Fig. 76). Dorsal to the upper fillet is the central tract containing fibres which arise in the cells of the cranial nerve nuclei, and travel to the optic thalamus.

The afferent impulses connected with the kinæsthetic and pressure sensations, with the sensations of heat, cold, and pain, as well as those connected with the sensation of hearing, all travel up through the tegmentum.

The **pyramidal fibres**, which come from the large pyramidal cells of the cerebral cortex, traverse the middle part of the crusta of the crus cerebri. From within outwards the arrangement of the fibres is as follows: those for the face and neck, those for the arm, trunk, and, externally, those for the leg.

Ventral to the substantia nigra is a bundle of fibres which arise in the cells of the nucleus caudatus, and travel down to arborise around cells in the pons.

Cerebellar Connections.—In the innermost portion of the crusta are the fibres which connect the frontal and parietal lobes of the cerebrum with the opposite half of the cerebellum. In the outermost parts of the crusta are the fibres which connect the temporo-sphenoidal and occipital lobes of the cerebrum with the opposite half of the cerebellum.

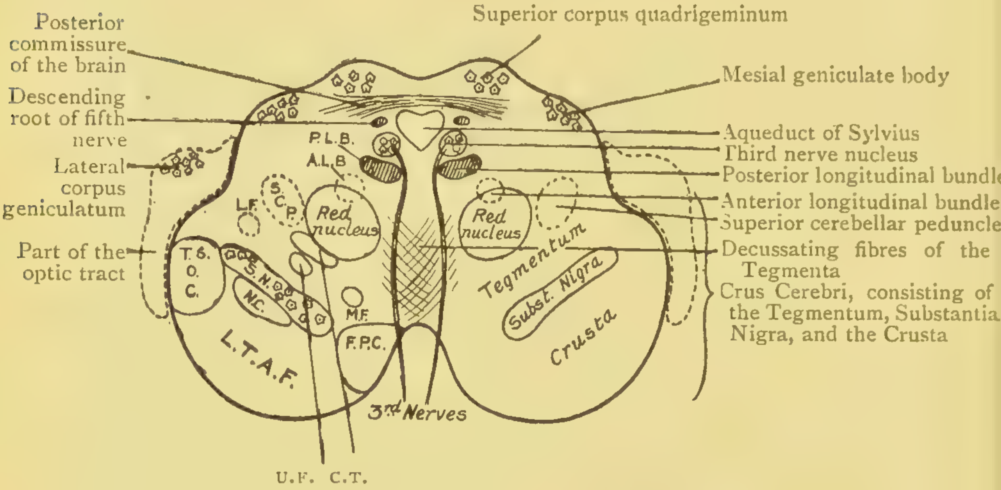

Superior corpus quadrigeminum
Posterior commissure of the brain
Descending root of fifth nerve
Lateral corpus geniculatum
Part of the optic tract
Mesial geniculate body
Aqueduct of Sylvius
Third nerve nucleus
Posterior longitudinal bundl
Anterior longitudinal bundle
Superior cerebellar peduncle
Decussating fibres of the Tegmenta
Crus Cerebri, consisting of the Tegmentum, Substantia Nigra, and the Crusta
P.L.B.
A.L.B
S.C.P.
L.F.
Red nucleus
Red nucleus
T.S.O.C.
S.N.
N.C.
M.F.
F.P.C.
L.T.A.F.
Tegmentum
Subst. Nigra
Crusta
3rd Nerves
U.F. C.T.

FIG. 76.—Diagram of a section across the mid-brain at the level of the anterior corpora quadrigemina.

L.F. = Lateral fillet with auditory fibres distributed to posterior corpus quadrigeminum (this is present only in a section of the mid-brain through the posterior corpora quadrigemina).
U.F. = Upper fillet distributed to the anterior corpus quadrigeminum.
M.F. = Mesial fillet distributed to the optic thalamus.
C.T. = Central tract containing afferent fibres from the cranial nerve nuclei travelling to the optic thalamus.
N.C. = Fibres which arise in the cells contained in the nucleus caudatus travelling down to the pons.
S. N. = Cells forming the substantia nigra; these receive collaterals from the fibres contained in the crusta.
F.A.T.L. = Pyramidal fibres from the face, arm, trunk, and leg areas of the cerebral cortex.
F.P.C. = Fibres connecting the frontal and parietal lobes with the contra-lateral half of the cerebellum.
T.S.O.C. = Fibres connecting the temporo-sphenoidal and occipital lobes with the contra-lateral half of the cerebellum.
A.L.B.—Anterior longitudinal bundle passing through the red nucleus.

The **substantia nigra** is situated between the tegmentum and the crusta. It consists of deeply pigmented nerve cells, which receive collaterals from the pyramidal fibres in the crusta.

The **red** or **tegmental nucleus** is situated above the substantia nigra, in close relationship with the superior cerebellar peduncle. The cells in the red nucleus receive fibres from the nucleus lenticularis of the corpus striatum (this last-named nucleus is a cell station for some fibres from the cortex cerebri), also from the anterior longitudinal bundle of the same side, and from the corpus dentatum of the opposite half of the cerebellum. The cells of the red nucleus give rise to nerve fibres which cross the median raphé in Forel's decussation in the mid-brain and descend into the pons. They travel through the medulla and form the rubro-spinal tract or Monakow's bundle, which continues down the spinal cord as the pre-pyramidal tract. These fibres finally arborise around the anterior cornual cells of the spinal cord.

THE CORPORA QUADRIGEMINA.

The Posterior Corpora Quadrigemina, or **Inferior Colliculi**, are composed of white matter with nerve cells in the middle. These cells receive fibres from the lateral fillet, which contains auditory fibres.

The Anterior Corpora Quadrigemina, or **Superior Colliculi**, consist of layers of nerve fibres and groups of nerve cells. These cells receive fibres from the upper fillet, from the ascending antero-lateral tract of Gowers, and from the optic tract (and consequently from nerve cells in both retinæ). The cells of the anterior corpus quadrigeminum give rise to fibres, some of which travel to the cells of the third nerve nucleus which lies ventral to the superior colliculus. Other fibres cross the middle line in the raphé, where they form the fountain decussation of Meynert, and after the crossing they help to form the opposite anterior longitudinal bundle. No fibres are given off from the cells of the corpora quadrigemina to the cortex cerebri (Schäfer).

The Cranial Nerve Nuclei, which exist in the mid-brain, are those of the third, fourth, and the accessory motor root of the fifth.

The Third Nerve Nucleus consists of groups of large nerve cells which lie just ventral to, and on either side of, the aqueduct of Sylvius. The fibres of the third nerve, which arise in these cells, pass forward and downwards to become superficial on the inner aspect of the crusta. According to Van Gehuchten, some of the fibres from the third nerve nucleus cross the middle line and leave in the third nerve of the opposite side (*vide* p. 671). The accessory root of the fifth nerve lies just above and external to the third nerve nucleus.

An extensive lesion involving one side of the mid-brain may cause complete paralysis of the third nerve of the same side, and paralysis of the opposite half of the face, opposite arm and leg. This is a condition known as "Weber's syndrome," and is one variety of "crossed paralysis."

√ **The Posterior Longitudinal Bundle**, or **the Vestibulo-motor Tract.**—This tract of nerve fibres extends from the optic thalamus through the mid-brain, pons, and medulla into the descending antero-lateral tract of the cord, from which its fibres arborise around the anterior cornual cells. In the mid-brain, the posterior longitudinal bundle lies ventral to the aqueduct of Sylvius; in the pons and medulla, it lies subjacent to the grey matter in the floor of the fourth ventricle. The third and fourth nerve nuclei are applied to its inner and dorsal aspect; the sixth nerve nucleus is present on its external aspect. The posterior longitudinal bundle receives fibres: (*a*) From the nucleus of the posterior longitudinal bundle, which is situated in the grey matter at the side of the third ventricle, just in front of the aqueduct of Sylvius, and well in front of the third nerve nucleus. (*b*) From the cells of the nucleus of Deiters (possibly from both sides). These fibres on reaching the bundle bifurcate, one branch ascending, the other descending. (*c*) From the cells constituting the sensory nucleus of the fifth nerve, from cells in the formatio reticularis of the mid-brain, pons, and medulla. All these fibres bifurcate, one branch ascending in the bundle and the other descending in the bundle, in a similar way to the fibres from the nucleus of Deiters. The posterior longitudinal bundle gives off collaterals to the third, fourth, and sixth nerve nuclei, and it is probably also connected with the nuclei of other cranial nerves. According to authorities, there are three important connections made through the posterior longitudinal bundle:—

1. Mendel believes that fibres from the oculo-motor nucleus are carried down in the posterior longitudinal bundle, and from this into the facial nerve for the supply of the upper portion of the orbicularis palpebrarum and the corrugator supercilii, bringing these muscles, therefore, under the control of the same nucleus as the levator palpebræ superioris (Cunningham).

2. Fibres from the hypoglossal nucleus may, by means of the posterior longitudinal bundle, reach the facial nerve, and through it the orbicularis oris. In this way the hypoglossal nucleus controls not only the tongue muscles, but also the sphincter of the mouth.

3. Duval and Laborde suggest that fibres from the sixth nerve nucleus ascend in the posterior longitudinal bundle to the mid-brain, and, crossing in the formatio reticularis, pass to that portion of the opposite third nerve nucleus which gives rise to those fibres which supply the opposite internal rectus muscle. This explains the fact that, if the sixth nerve nucleus is stimulated, the eyes are turned to the side of irritation; in other words, in the case of an irritative pontine lesion there is conjugate deviation of the eyes towards the side of the lesion.

✓ **The Anterior Longitudinal Bundle, or the Tecto-spinal Tract.**—This tract lies on the ventral and lateral aspect of the posterior longitudinal bundle, and throughout is in close apposition to the posterior longitudinal bundle. Anteriorly, it receives fibres from the cells of the grey matter of the opposite superior corpus quadrigeminum. These fibres pass obliquely downwards into the tegmentum, encircle the grey matter around the aqueduct of Sylvius, and cross in the median raphé, where they form the fountain decussation of Meynert. After crossing the middle line they help to form the anterior longitudinal bundle. The fibres of this bundle give off collaterals to the third, fourth, and sixth nerve nuclei, and also to the red nucleus; they traverse the pons and medulla, and enter the spinal cord; some of the fibres become mixed with the fibres in the rubro-spinal tract, while others enter the descending antero-lateral tract of Löwenthal.

CHAPTER XLII.

THE CORPORA GENICULATA.

The external corpus geniculatum contains nerve fibres and nerve cells. The nerve cells receive fibres from the optic tract, which are the terminations of some of the second visual neurones. The cells of the external corpus geniculatum give rise to fibres which traverse the optic radiation of the internal capsule of the corpus striatum, and eventually pass to the grey matter around the calcarine fissure of the occipital cortex; these are the third set of neurones of the visual tract.

The internal corpus geniculatum contains cells which receive fibres from the auditory nuclei of both sides of the brain; these fibres travel up in the lateral fillet. The internal corpora geniculata are connected together by the commissure of von Gudden.

THE OPTIC THALAMUS.

The optic thalamus forms the side of the third ventricle and part of the floor of the lateral ventricle. On its outer side is a covering of white matter, but internally it is divided by white laminæ into nuclei which contain nerve cells. These internal portions are the anterior, the mesial, the lateral nuclei, and the pulvinar.

The optic thalamus receives fibres: (1) From the internal capsule, which connect it with the cerebral cortex; (2) from the mesial fillet, which connect it with the nucleus gracilis and nucleus cuneatus of the opposite half of the medulla; these fibres constitute the second afferent neurones in the course of the conducting path from the cord; (3) from the central path of the fifth nerve of the opposite side (Schäfer); (4) from the contra-lateral corpus dentatum by the superior cerebellar peduncle; (5) from the optic tract: these fibres pass to the pulvinar. The nerve cells in the optic thalamus give rise to fibres which pass out into the white matter of the brain, and eventually reach the frontal, parietal, temporo-sphenoidal, and occipital lobes. The fibres which pass to the cortex cerebri are the third set of afferent neurones, and constitute the thalamo-cortical connections. The fibres which pass to the grey matter around the calcarine fissure of the occipital cortex are those which represent the third afferent neurones on the visual tract.

THE CORPUS STRIATUM.

The corpus striatum lies in the deep part of the cerebral hemisphere, and consists of alternate layers of grey and white matter. These constitute the nucleus caudatus, the internal capsule, the nucleus lenticularis, and the external capsule (*vide* Fig. 77).

The Nucleus Caudatus.—This consists of nerve cells which receive connections from the adjacent internal capsule, *i.e.* from the collaterals of the pyramidal projection fibres. The cells in the nucleus caudatus give rise to fibres which travel down to, and arborise around, cells present in the substantia nigra of the crus cerebri, and to other fibres which lie below the substantia nigra, and which arborise around nerve cells in the pons Varolii.

The Nucleus Lenticularis.—This nucleus lies between the internal and external capsules, and is divided by white nerve fibres into three zones of grey matter. The inner two constitute the globus pallidus, and the outer one the putamen. The nerve cells upon its inner aspect receive connections from some of the fibres of the internal capsule, *i.e.* from the collaterals which belong to the projection fibres from the large pyramidal cells of Betz.

The Internal Capsule.—This consists of an anterior limb, genu, and a posterior limb. In a horizontal section the anterior limb lies between the nucleus caudatus and the nucleus lenticularis; the genu is situate between the nucleus caudatus and the optic thalamus, and the posterior limb lies between the optic thalamus and nucleus lenticularis.

The *afferent fibres* (thalamo-cortical) are present in the hind part of the posterior limb, and also extend forwards, being mixed with the efferent fibres.

The *efferent fibres*, which are the projection fibres from the Betz cells of the excitable area of the cerebral cortex, traverse the anterior limb, the genu, and the posterior limb of the internal capsule in the following order from before backwards: Fibres for the eyes and head in the anterior limb just in front of the genu, those for the mouth and tongue at the genu, those for the shoulder, elbow, wrist, fingers, trunk, hip, knee, and toes in the posterior limb of the internal capsule (Beevor and Horsley).

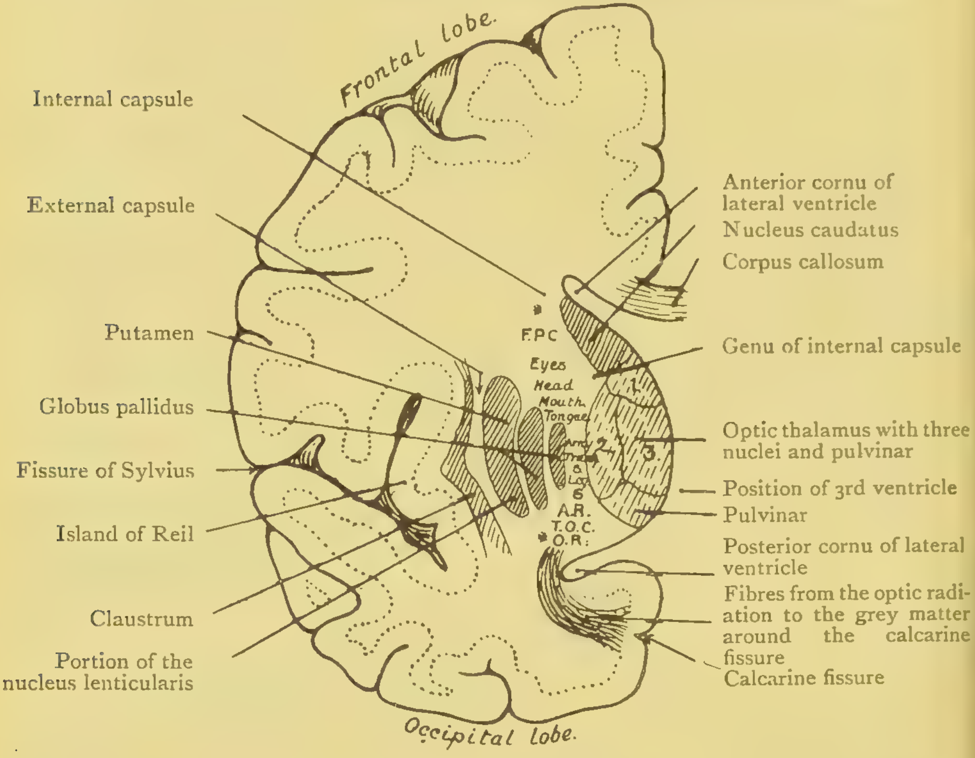

Frontal lobe
Internal capsule
External capsule
Putamen
Globus pallidus
Fissure of Sylvius
Island of Reil
Claustrum
Portion of the nucleus lenticularis
Anterior cornu of lateral ventricle
Nucleus caudatus
Corpus callosum
Genu of internal capsule
Optic thalamus with three nuclei and pulvinar
Position of 3rd ventricle
Pulvinar
Posterior cornu of lateral ventricle
Fibres from the optic radiation to the grey matter around the calcarine fissure
Calcarine fissure
*
F.P.C
Eyes
Head
Mouth
Tongue
1
2
3
a
Leg
6
A.R.
T.O.C.
* O.R.
Occipital lobe

FIG. 77.—Diagram of a horizontal section through the brain cutting the corpus striatum and optic thalamus.

The position of the internal capsule is marked between the two * *

F.P.C. = Position of fronto-parieto-cerebellar fibres.
T.O.C. = Position of temporo-sphenoidal and occipito-cerebellar fibres.
S. & s. = Position of afferent fibres.
O.R. = Position of fibres of optic radiation.
A.R. = Position of fibres of auditory radiation.

√**Cerebellar Connections.**—In the most anterior part of the anterior limb of the internal capsule are fibres which connect the frontal and parietal lobes with the opposite half of the cerebellum; and in the posterior limb of the internal capsule, situated immediately behind the auditory radiation, are fibres which connect the temporo-sphenoidal and occipital lobes with the opposite half of the cerebellum.

Special Sense Fibres.—Immediately behind the temporo-sphenoidal and occipital cerebellar fibres is the optic radiation. Most of these fibres arise from cells in the pulvinar of the optic thalamus and in the external corpus geniculatum (the third set of visual neurones). They traverse the internal capsule, travel thence into the corona radiata to the grey matter around the calcarine fissure on the mesial aspect of the occipital cortex. In front of the temporo-sphenoidal and occipito-cerebellar fibres is the auditory radiation, the fibres of which traverse the corona radiata to gain the superior convolution of the temporo-sphenoidal lobe (the auditory centre).

The blood supply of the corpus striatum is derived from the middle cerebral artery. Near its commencement it gives off numerous basal branches, which enter the anterior perforated space and ascend to the corpus striatum. These vessels are called the lenticular, lenticulo-striate, and the lenticulo-optic, according to their distribution. Of these the lenticulo-striate artery of the left side is that which is most frequently the seat of rupture (cerebral hæmorrhage), and when this occurs the nerve fibres traversing the internal capsule are involved. If, for example, the whole of the fibres of the internal capsule of the *left* side of the brain are damaged by a lesion, there will follow as a consequence, conjugate deviation of the head and eyes to the left (side of lesion), paralysis of the *right* side of the face, *right* arm, and *right* leg, *right-sided* hemianæsthesia and *right* hemianopia. The muscles of the trunk escape because they are equally bilaterally represented on the cerebral cortex (Broadbent's law).

CHAPTER XLIII.

THE CEREBRAL CORTEX.

THE surface of the cerebrum is rendered very irregular by the presence of the *convolutions or gyri*, which are separated from each other by *fissures or sulci*. The surface pattern produced by these convolutions and fissures is more or less the same in all human brains. It is by means of these convolutions and fissures that the grey matter of the cortex cerebri is enormously increased, and the vascular pia mater which dips into the various fissures is similarly increased in extent.

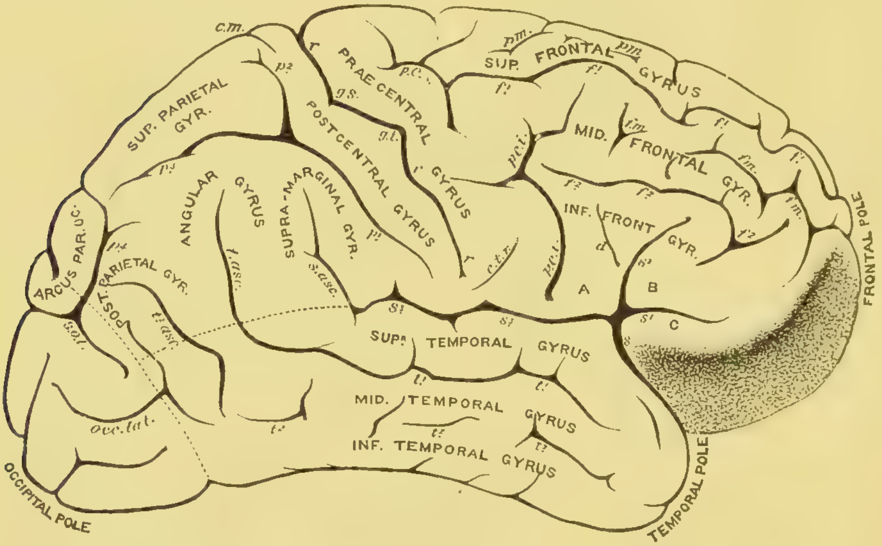


FIG. 78.—The convolutions and fissures of the outer aspect of the right cerebral hemisphere. (*After* Cunningham.)

s. = Fissure of Sylvius.
s.^{1} = Anterior horizontal limb of Sylvian fissure.
s.^{2} = Ascending limb of Sylvian fissure.
s.^{3} = Posterior horizontal limb of Sylvian fissure.
r. = Fissure of Rolando.
c.m. = Calloso-marginal sulcus.

The cerebral cortex may be considered to be a complex sensori-motor mechanism, or a large sensori-motor ganglion. It receives all the afferent impulses which enter into consciousness, so that it may be said that kinæsthetic and cutaneous *sensations* arise there.

In a similar way, *sensations* of heat, cold, pain, and visual sensations, auditory sensations, sensations of smell, taste, hunger, thirst, etc., all arise in the cortex cerebri. The cells of the motor area originate movement. The cells of the receptive areas, and those of the areas where movement is originated, are associated together in their harmonious working. There are, however, also in the cortex cerebri special associational areas (*vide* Fig. 80).

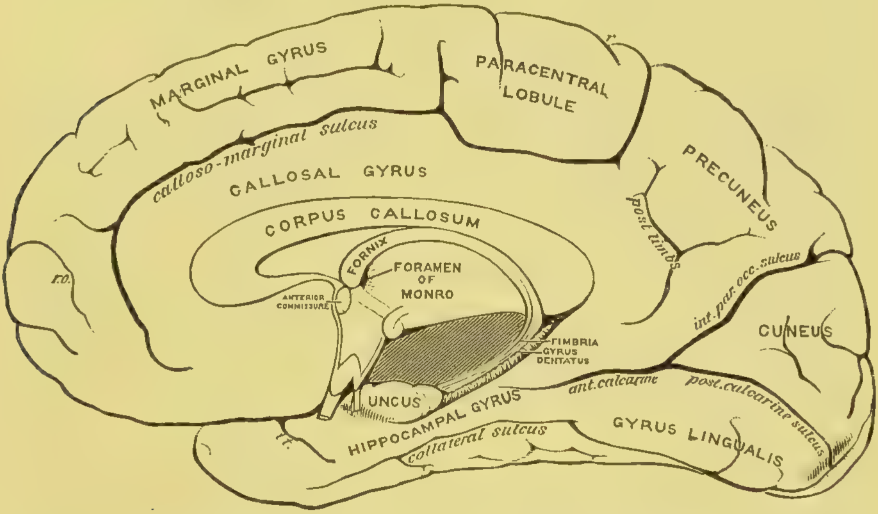


FIG. 79.—The convolutions and fissures on the mesial aspect of the right cerebral hemisphere. (*After* Cunningham.)

r. = Fissure of Rolando.
r.o. = Rostral sulcus.
i.t. = Incisura temporalis.

THE EXCITABLE AREAS OF THE CEREBRAL CORTEX.

The psychomotor area is situated in the ascending frontal convolution, or the pre-Rolandic convolution, which lies immediately in front of the fissure of Rolando. It is sometimes called the "Betz-cell area," because in it are the large pyramidal cells described by Betz. This area is also known as the excitable region of the cerebral cortex, because, if it is stimulated electrically by a weak faradic current, or pathologically by tumours, certain movements result. If portions of this area are excised a certain amount of paralysis follows. The motor areas, which have been mapped out on the ascending frontal convolution, are represented in the diagram (Fig. 80) of the cerebral cortex. From below upwards the movements (*not* muscles) which are represented are as follows: Those of the tongue, lips, larynx, all together near the fissure of Sylvius, then those of the face and neck, then those of the arm in the middle portion of the ascending frontal convolution, then those of the trunk, and lastly, uppermost are those of the leg.

It is important to note that here movements are represented, and not muscles. On the cerebral cortex these areas, representing movements of the opposite side of the body, are not so well defined as appears in the diagram of the cortex cerebri; moreover, these areas are not confined to the outer surface of the ascending frontal convolution, but extend deeply on the surface of the frontal lobe in the fissure of Rolando; the upper areas extend also on to the mesial aspect of the brain. Although, when these areas are experimentally excited, movements occur on the opposite side of the body, yet, in normal circumstances, the Betz cells, which originate efferent impulses resulting in movement, appear to depend upon

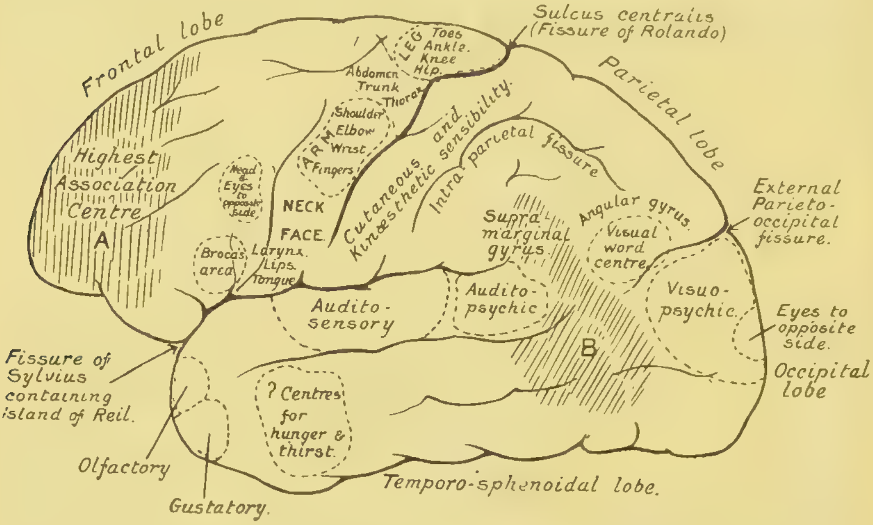


FIG. 80.—Diagram of the left half of the outer side of the cerebral cortex to represent cerebral localisation.

A = A great association area connected with the "motor" aspect of the cerebral functions (complex prefrontal association centre).

B = The posterior region of association connected with the "sensorial" aspect of the cerebral functions (parieto-temporal association centre).

The least important association centre is situated in the island of Reil.

afferent impulses reaching them from the periphery. The absolute dependence of the activity of the pyramidal or Betz cells upon the afferent stimuli, which in normal circumstances reach them, has been shown by Mott and Sherrington. The posterior nerve roots of the brachial plexus of a monkey have been divided, with the result that motor paralysis in the arm, especially for finer movements, occurred. The arm area of the opposite side of the cerebral cortex was subsequently excited electrically, with the result that movements in the arm were at once induced. This experiment shows that, in normal circumstances, the cells of the excitable area of the cerebral cortex need the arrival of an adequate stimulus in order that they may discharge energy.

Almost immediately in front of the face area there is a portion of the cortex which appears to receive afferent impulses from the eyelids and eyeballs. It is said to be particularly concerned in the association of the eye movements with the equilibrium of the body, and the maintenance of the erect posture If the anterior part of this area is excited, the result is a conjugate deviation of the eyes to the opposite side, *i.e.* if the area upon the left side of the cortex is stimulated, the eyes are turned to the right; in other words, if this area is stimulated by a lesion, such as a tumour, there follows a conjugate deviation of the eyes *away* from the side of the lesion.

At the extreme posterior part of the cortex cerebri in the occipital lobe there is also an area which, if excited, causes a conjugate deviation of the eyes to the opposite side, *i.e.* away from the side of excitation.

Broca's Area in a right-handed individual is present in the posterior portion of the *left* inferior frontal convolution. The cells of this area appear to be intimately connected with the adjacent areas for the movements of the tongue, lips, and larynx, and it may be that Broca's area is a highly developed co-ordinating area, which presides over the efferent impulses which leave the areas of the tongue, lips, and larynx, and which, when adequately co-ordinated, result in speech. If Broca's area is damaged by a hæmorrhage, or a tumour, the result is motor aphasia or aphemia. Recently some doubt has been expressed with regard to the presence of such a special co-ordinating centre as that just described. Marie considers that Broca's area is not connected with speech, but that

"Wernicke's area," namely, the supra-marginal and angular gyri (visual word centre) and the posterior part of the superior temporo-sphenoidal lobe (auditory word centre) are the site of the lesion which results in true aphasia. He also considers that a lesion of the nucleus lenticularis involving the external capsule, and possibly the anterior part and genu of the internal capsule, results in anarthria (inability to articulate). He further considers that the aphasia of Broca, due as Broca suggested to a lesion of the posterior portion of the inferior frontal convolution of the left side of the brain in a right-handed individual, is really due to a lesion of the "area of Wernicke" (the sensory aphasia of Wernicke), together with a lesion of the nucleus lenticularis and the adjacent portion of the internal and possibly the external capsule (anarthria). In short, it may be stated that, as the result of extensive investigations, Marie doubts the presence of a well localised speech centre such as described by Broca, but seems to be of the opinion that aphasic disorders are brought about by local losses of the functional continuity between various cortical centres which, when working harmoniously together, constitute the speech mechanism. In a general way, it may be said that, in the cerebral cortex, there are four centres which constitute the physical bases of the speech mechanism,—the auditory, the visual, the articulatory (tongue, lips, larynx), and the cheirographic (hand) centres.

The Course of a Motor Impulse.

The efferent impulses which originate in the psycho-motor area of the cerebral cortex, and which result in movement of the muscles on the opposite of the body, travel through the nervous system as follows:—

They start in the pyramidal cells of Betz, travel down in the long projection fibres through the corona radiata into the internal capsule of the corpus striatum, thence through the pyramidal fibres in the crusta of the crus cerebri to the longitudinal fibres in the pons. In the pons the impulses for the face cross to the opposite side in order to gain the facial nucleus, and thence along the facial nerve in order to gain the facial muscles. The motor impulses for the arm and leg travel directly through the pons to the medulla, in the lower anterior part of which they cross to the opposite side in the decussation of the pyramid in order to gain the crossed pyramidal tract. The impulses leave the pyramidal tract and travel into the grey matter of the cord in order to gain the nerve cells at the base of the posterior cornua. The impulses then travel to the multipolar nerve cells in the anterior cornua. The motor impulses leave the spinal cord by the anterior nerve roots, and travel through the motor nerves and motor portions of mixed nerves to the motor end-organs in the muscle fibres. It will be observed that a motor impulse has to traverse at least three neurones: (1) The upper motor neurone, from the motor part of the cortex to the base of the posterior cornu. (2) The short intermediate neurone, from the base of the posterior cornu to the anterior cornual cells. (3) The lower motor neurone, from the large multipolar nerve cell in the anterior cornu to the motor end organ in the interior of a transversely striated muscle fibre.

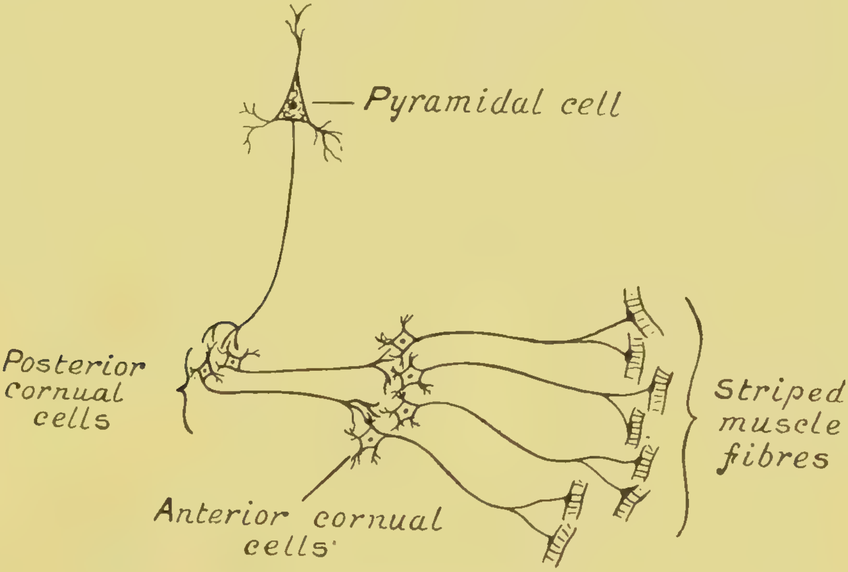


FIG. 81.—Diagram to show a pyramidal cell controlling many striped muscle fibres.

It is by means of these three motor neurones that a single pyramidal cell of the cerebral cortex may influence a large number of muscle fibres. The projection fibre of a pyramidal cell arborises around *at least* two posterior cornual cells, and the fibre from each of these cells arborises around *at least* two multipolar nerve cells, and a branching projection fibre from a multipolar nerve cell, goes to *at least* two motor end organs. This arrangement is demonstrated in Fig. 81.

THE RECEPTIVE AREAS OF THE CEREBRAL CORTEX.

Kinæsthetic and cutaneous impulses, which give rise to sensations, are received in the ascending parietal convolution just behind the fissure of Rolando. The afferent impulses which gain this area are connected with the cells of the motor area in front by means of association cells. The motor and sensory areas around the fissure of Rolando constitute the kinæsthetic, sensori-motor, or Rolandic area, and these areas are intimately connected, as is shown by the fact that, in cases of focal epilepsy, due to irritation of a portion of this area by a tumour, or to a piece of bone driven into the brain (depressed fracture), before the irregular convulsive movement occurs in the part of the body, corresponding with the motor area irritated, the individual frequently complains of definite sensations referred to the part which is about to become convulsed. These subjective sensations appear to be due to the irritant stimulating the cells of the kinæsthetic area of the cortex.

Cutaneous sensibility is also represented on the mesial aspect of the brain, in the callosal gyrus situated immediately above the corpus callosum.

The visual areas are present in the occipital lobes of the brain. The visual receptive area is situated around the calcarine fissure on the mesial aspect of the brain. This area is known as the visuo-sensory area. It is in this area that the afferent impulses, set up by light rays falling upon a receptive retina, are sensed. A lesion of the whole of the *left* cuneate lobe causes right hemianopia in both visual fields. If the lesion is limited to the portion of the left cuneus *above* the calcarine fissure, the result is blindness in the right *lower* quadrant of both visual fields. If the lesion in the left cuneus is below the calcarine fissure, the result is blindness in the right *upper* quadrant of both visual fields. These are varieties of quadrantic hemianopia. Around the visuo-sensory area on the mesial aspect of the brain, and on the external surface of the occipital lobe, is the higher visual area, or the association visual area; this is called the visuo-psychic area, and in it, in all probability, the import of things seen is recognised. In a right-handed individual there is in the angular gyrus on the left side of the cortex the most highly evolved visual area, called the "visual word area," by which the meaning of written or printed words is appreciated. This is a matter of higher association. If a lesion occurs in the visual word centre the result is inability to read (alexia).

The auditory areas are present in the superior temporo-sphenoidal lobes. In the middle portion of the superior temporo-sphenoidal lobe is the audito-sensory centre, and immediately behind it is the more highly developed audito-psychic and auditory word centre.

The olfactory and gustatory centres are present in the anterior part of the temporo-sphenoidal lobe, but they extend more definitely on the deep surface of the brain. Just behind these centres, upon the external surface of the brain, there are, in all probability, centres associated with the organic sensations of hunger and thirst. Injuries and tumours in this region have sometimes been associated with a voracious appetite and intense thirst, persisting for weeks (Purves Stewart).

THE ASSOCIATION AREAS OF THE CORTEX.

It must be remembered that, unless part of the cortex cerebri has been removed, or has become diseased, the cerebral cortex functions *as a whole*, and consequently it may be considered as a great association area. According to Flechsig, however, there are three particular association centres. The *middle* one in the grey matter of the island of Reil, the *posterior* one in the posterior portion of the parieto-temporal region (this appears to be the region of association of "sensorial" function), and the *anterior* one in the most anterior part of the frontal lobes called the prefrontal region. This area of the brain exhibits the greatest complexity, and appears to be the chief association centre concerned with the motor aspect of the cerebral functions. It is, in all probability, the centre of highest control, and therefore the centre for *inhibition*, and as a consequence it must of necessity be the centre for that highest and latest evolved function of the brain, namely, that of *voluntary attention*. "The prefrontal region is the highest zone of association, and insanity depends on sub-evolution or dissolution of this region. In the case of sub-evolution, the patient may be permanently idiotic or imbecile, permanently or temporarily insane, or liable to the onset of insanity; in the case of dissolution, according to its degree, the patient suffers from a corresponding grade of permanent dementia" (J. S. Bolton).

All these association centres of Flechsig are particularly well developed in the human brain.

The various regions of the cerebral cortex are connected together by means of association fibres. The following diagram shows the position of some of these more important association fibres.

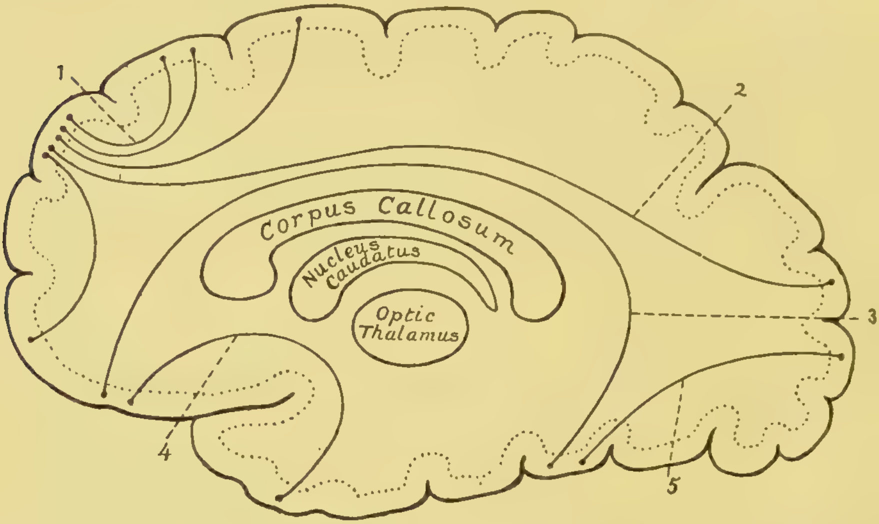


FIG. 82.—Diagram to show the position of some of the association fibres of the cerebrum. (*After* Halliburton.)

1=Fibres between adjacent convolutions.
2=Fibre between the frontal and occipital convolutions.
3=Fibre between the frontal and temporo-sphenoidal convolutions.
4=Fibre between the frontal and temporo-sphenoidal convolutions.
5=Fibre between the occipital and temporo-sphenoidal convolutions.

The Histological Characters of the Cortex Cerebri.

The grey matter of the cerebral cortex may be subdivided into five layers, which are common to the whole cortex cerebri, although in different regions they are somewhat modified.

The following is a brief description of the five layers or laminæ of the cortex (after J. S. Bolton).

Lamina 1, or the Outer Fibre Lamina.—This is sometimes called the outer molecular layer. It consists of a superficial layer of medullated nerve fibres which run parallel to the surface of the brain; amongst these fibres are neuroglial and glial cells, and the pluripolar or horizontal cells of Cajal. This layer is present at the fourth month of fœtal life.

Lamina 2, or the Outer Cell Lamina.—This contains a few large but many medium-sized and small pyramidal cells; these are in all probability association cells. Amongst them is the thin fibre band known as the outer line of Baillarger.

This is the last cell layer of the cerebral cortex to develop during the process of lamination. In the adult it is the most prominent layer of the cortex, and it eventually becomes thicker than the next three layers together.

Lamina 3, or the Middle Cell Lamina.—This is the granular layer, and consists of small pyramidal cells with round nuclei. It is considered to be a sensory layer. In point of time it is the second layer of the cortex to develop, and is produced during the sixth month of fœtal life.

Lamina 4, or the Inner Fibre Lamina.—This constitutes the inner layer of nerve fibres, or the inner line of Baillarger. Between the fibres are small groups of pyramidal cells, and frequently solitary cells. This layer develops at the sixth month of fœtal life.

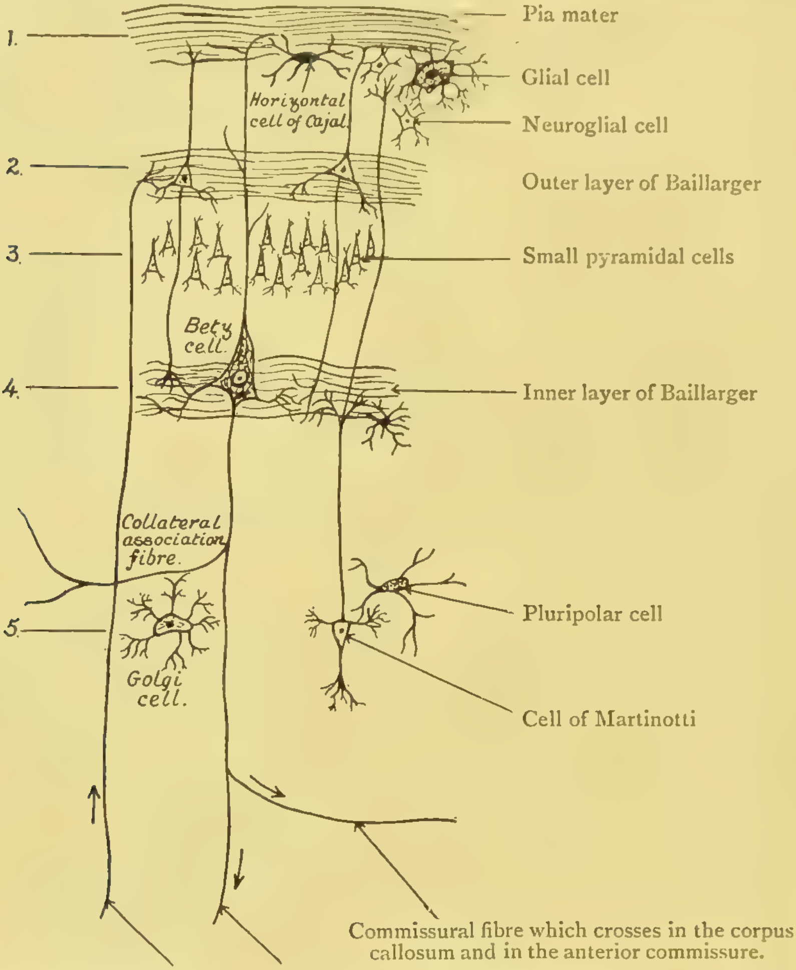
Lamina 5, or the Inner Cell Lamina.—This consists of polymorphic cells, amongst which are irregular cells with many branched processes (Golgi cells), pyramidal cells with base and axon turned towards the surface of the brain (cells of Martinotti), and ovoid cells with many long branches. This is the first cell layer to appear, and is of constant average thickness.

The characteristics of the psycho-motor area are:—

1. The middle cell lamina forms a very thin granular layer.
2. The inner fibre lamina contains many large pyramidal cells of Betz. The psycho-motor area is sometimes called the "Betz-cell" area.

The visuo-sensory area which is present around the calcarine fissure, and which is the projection centre for visual impressions, reaches maturity before the visuo-psychic and prefrontal areas, and the characteristics of its structure are as follows: The outer fibre lamina and the outer cell lamina have the same structure as is common to the other regions of the cortex. The middle cell lamina, or granular layer, becomes hypertrophied.

The fibres which represent the outer layer of Baillarger become much increased, so that a very thick mass of medullated nerve fibres is present in this situation; these fibres form the characteristic "line of Gennari," amongst the fibres of which are the solitary cells of Meynert. Interpolated between the "line of Gennari" and the outer cell lamina is an outer



Commissural fibre which crosses in the corpus callosum and in the anterior commissure.

Afferent fibre from the optic thalamus, which branches in the superficial layer of the cerebral cortex.

Projection fibre of the pyramidal and cortico-pontine tract. This fibre gives off collaterals to the corpus striatum and to the optic thalamus.

FIG. 83.—Diagram to represent the structure of the psycho-motor area of the cerebral cortex.

1. = Outer fibre lamina.
2. = Outer cell lamina.
3. = Middle cell lamina (granular layer).
4. = Inner fibre lamina.
5. = Inner cell lamina (polymorphic layer).

layer of granules. The middle cell lamina is sometimes described as being hypertrophied, and split by the medullated nerve fibres which form the line of Gennari, but it appears that the inner layer of granular cells represents the middle cell lamina, the line of Gennari represents a hypertrophied outer line of Baillarger, and the outer layer of granular cells is an addition to this region.

The inner fibre lamina, or inner line of Baillarger, contains a few solitary cells of Meynert. These cells are like the Betz cells, their axons pass along association tracts to the motor eye centre of the frontal region, and some also pass to the region of the corpora quadrigemina. The layers of the cortex of the visuo-sensory area then, from without inwards, are:—

1. Outer fibre lamina.
2. Outer cell lamina.
3. *Outer layer of granules.*
4. *Line of Gennari with solitary cells of Meynert.*
5. *Inner layer of granules* (the hypertrophied middle cell lamina).
6. Inner fibre lamina *with solitary cells of Meynert.*
7. Inner cell lamina (polymorphic cells).

In cases of congenital, or long standing, blindness the outer layer of granules and the line of Gennari are either not developed or are decreased. This is due to a want of development, or to atrophy of the optic radiations.

The visuo-psychic area is present upon the mesial surface of the occipital lobe around the visuo-sensory area, and extends on to the external surface of the occipital lobe. This area reaches maturity later than the visuo-sensory area, but earlier than the prefrontal area. It is five layered, but the middle cell lamina generally becomes hypertrophied; it contains no line of Gennari. In cases of congenital or of long-standing blindness there is no modification in lamination, and the general structure remains like that common to the whole cerebral cortex.

The prefrontal area is five layered, and is the last portion of the cerebral cortex to reach maturity. The outer cell lamina varies measurably in depth in the brains of normal individuals, and it appears to vary in thickness *directly* with the mental capacity of the individual. The outer cell lamina is the most important feature of the human adult cerebral cortex, and it is the last layer to develop.

The grey matter of the island of Reil is characterised by the presence of layers of spindle-shaped cells lying internal to the inner cell lamina between it and the white matter. This layer of grey matter is called the claustrum.

The Evolution of the Brain.

The primitive vertebrate brain consists of the three primary cerebral vesicles, which become further subdivided as follows :—

First Primary Vesicle	Prosencephalon (cerebral hemispheres and corpus striatum). Thalamencephalon(optic thalamus).
Second Primary Vesicle	Mesencephalon (crura cerebri and corpora quadrigemina).
Third Primary Vesicle	Metencephalon (pons and cerebellum). Myelencephalon (medulla oblongata).

The five secondary vesicles, namely, the pros-, thalamen-, mes-, met-, and myel-encephalon form the primitive brain, as is seen in the dogfish. This "old" brain is sometimes known as the palæ-encephalon (Edinger). From the prosencephalon the cerebral hemispheres develop and form the "new" brain or neo-encephalon. The characteristic of the neo-encephalon is the presence of a large amount of grey matter. The first portion of the grey matter of the cerebral cortex to develop, in the lower vertebrate types, is the part associated with the function of smell, and this is called the old cortex or archipallium. That which develops later is that associated with the higher functions of the brain, and forms the new cortex or cerebral cortex. This is peculiar to mammals, and is called the neopallium (Elliott Smith).

The neopallium increases in amount and complexity as the mammalian scale is ascended, and in man it constitutes practically the whole of the cerebral cortex. The neopallium is a most highly differentiated sensori-motor ganglion, the functions of which, according to J. S. Bolton, may be enumerated as follow :—

1. The reception of sensorial stimuli. This occurs chiefly in the posterior portion of the cerebral cortex, in which too are the zones of sensory association.

2. The conservation of associative memory.

3. The performance of the highest psychic processes, the result of association.

4. The evolution of motor phenomena which serve as the

objective indications of the performance of psychic processes (mental processes have motor consequences); these apparently occur in the anterior portion of the cortex, and are the result of the association of sensations brought about by afferent impulses.

The **archipallium** is primarily built up of two cell laminæ, which are homologous with the inner and middle cell laminæ of the neopallium. It is possible that these layers serve the physical basis of the "instinctive" mental processes.

The **neopallium** is characterised by the presence of the outer cell lamina, which contains pyramidal cells; this lamina is the physical basis of psychical processes (Bolton).

The Functions of the Cell Laminæ of the Neopallium or Cortex Cerebri.

According to the researches of J. S. Bolton, the inner cell lamina, or the fifth layer of the cerebral cortex, is the first layer to develop. This layer is of constant average depth, and is well developed in the lower mammalia. The inner cell lamina, in association with the superimposed inner fibre layer, subserves the lower instinctive and voluntary activities of the animal, and in this way is a lower level cerebral basis for carrying on its animal or organic functions, such as attending to its own wants, feeding, excretion, etc.

The middle cell lamina, or third layer of the cerebral cortex, develops second in point of time. This granular layer is primarily receptive for the afferent impulses which arrive through the sensory neurones by way of the optic thalamus, and also for those which arrive from other regions of the cerebrum.

The outer cell lamina is the last layer of the grey matter to develop, and it is the first to undergo retrogression. It subserves the psychical or the associational functions of the cerebrum. These associational functions are least important in the visuo-sensory area or the projection sphere. They are more important, however, in the visuo-psychic area, or the region of lower association, and these functions are pre-eminent in the prefrontal area, or the centre of highest association; that is, *memory* and *thought*, the result of active attention.

CHAPTER XLIV.

THE CEREBELLUM.

The connections which the cerebellum makes with the other portions of the central nervous system are numerous; they may, however, be conveniently divided into two groups: (1) the afferent fibres to the cerebellum, and (2) the efferent fibres from the cerebellum to other regions of the central nervous system.

I. THE AFFERENT FIBRES TO THE CEREBELLUM.

A. **From the Spinal Cord** (the ascending spino-cerebellar neurones).

(i) From the ipso-lateral column of Clark, through the direct cerebellar tract, restiform body, inferior cerebellar peduncle to the vermis.

(ii) From the contra-lateral and the ipso-lateral column of Clarke, through the ventral cerebellar tract of Gowers, medulla, and pons, and back through the superior cerebellar peduncle to the vermis.

B. **From the Medulla.**

(i) From the ipso-lateral nucleus gracilis and nucleus cuneatus, through the restiform body and inferior cerebellar peduncle to the vermis.

(ii) From the contra-lateral nucleus gracilis and nucleus cuneatus, through the median raphé, external arcuate fibres, restiform body, and inferior cerebellar peduncle to the vermis.

(iii) From the ipso-lateral olivary nucleus, through the restiform body and inferior cerebellar peduncle to the vermis.

(iv) From the contra-lateral olivary nucleus, through the median raphé, internal arcuate fibres between the two inferior olives, restiform body, and inferior cerebellar peduncle to the vermis.

C. From the Pons Varolii.

(i) From the ipso-lateral vestibular nucleus, through the middle cerebellar peduncle to the vermis.

(ii) From the ipso-lateral vestibular nucleus, through the nucleus of Deiters, which is a cell station for the vestibular fibres, thence by the internal restiform body to the vermis.

(iii) From the contra-lateral nuclei pontis, through the superficial transverse fibres of the pons, thence by the middle cerebellar peduncle to the vermis.

D. From the Contra-lateral Cerebral Cortex.

(i) From the contra-lateral cerebral cortex by way of the contra-lateral optic thalamus and the ipso-lateral superior cerebellar peduncle to the vermis.

II. THE EFFERENT FIBRES FROM THE CEREBELLUM.

The flask-shaped cells of Purkinje present in the cerebellar cortex give rise to fibres which are efferent in function, and travel to the adjacent corpus dentatum, which is a local cell station (cerebello-dentate neurones). The cells in the corpus dentatum receive collaterals from fibres which traverse the inferior cerebellar peduncle.

The cells in the corpus dentatum give rise to fibres which pass to

(i) The ipso-lateral nucleus of Deiters, which gives rise to fibres which pass to the posterior longitudinal bundle of the same side, and so make connections with the nuclei of origin of the third, fourth, and sixth, and other cranial nerves, and possibly also fibres from the nucleus of Deiters pass across the median raphé of the pons to reach the posterior longitudinal bundle of the other side, and through this contra-lateral posterior longitudinal bundle reach the opposite third, fourth, and sixth, and other cranial nerve nuclei. The cells of the nucleus of Deiters also give rise to fibres which travel down the spinal cord, forming the vestibulo-spinal fibres in the antero-lateral descending tract which connect with the anterior cornual cells.

(ii) The contra-lateral nuclei pontis by way of the middle cerebellar peduncle, and the superficial transverse fibres of the pons.

(iii) The contra-lateral mid-brain and pons by way of the superior cerebellar peduncle, and make connection with the optic thalamus (dentato-thalamic neurones), third nerve nucleus, and tegmental or red nucleus. From these fibres of connection descending collaterals are given off which travel back to the pons to make connection with other local nuclei. The fibres which get to the optic thalamus make cell stations with the cells contained therein, and these cells give rise to new fibres which travel to the cerebral cortex (thalamo-cortical neurones).

THE STRUCTURE OF THE CEREBELLAR CORTEX.

The surface of the cerebellum is covered by pia mater, which carries the blood vessels which are distributed to the subjacent grey matter of the cerebellum. The cerebellar cortex is of similar structure throughout, and is described as consisting of three layers as follows:—

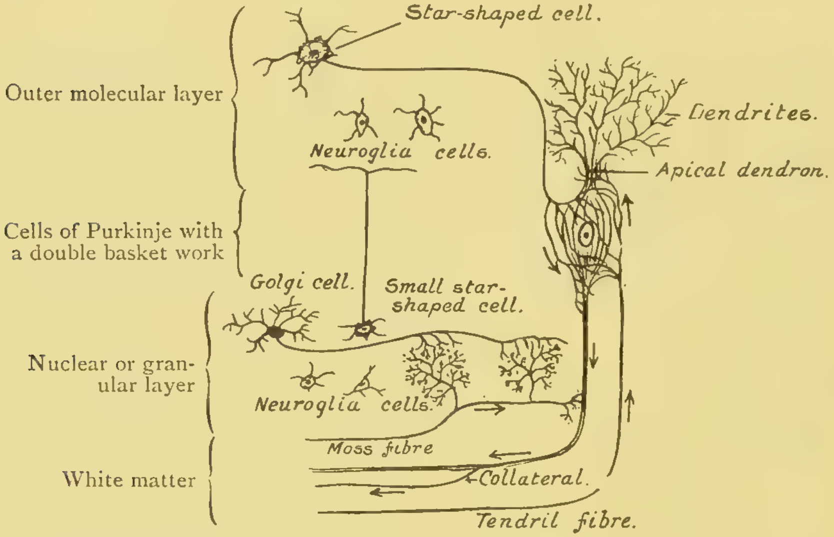


FIG. 84.—Diagram to represent the structure of the cerebellar cortex.

1. **The Outer Molecular Layer.**—This consists of irregular star-shaped cells and neuroglial cells. The star-shaped cells give rise to axons, which travel into the next layer and arborise around the bodies of the cells of Purkinje. Ramifying in this layer are the dendrites of the cells of Purkinje, and the branching axons from the small star-shaped cells from the subjacent nuclear layer.

2. **The Flask-shaped Cells of Purkinje.**—These cells are

closely set together, forming a single row. The apical dendron spreads out in a plane which is transverse to the direction of the lamellæ of the cerebellum, and breaks up into many branching dendrites which ramify in the outer molecular layer. The fibrillated axon, which is continuous with the neuro-fibrillæ of the body of the cell, passes down through the nuclear layer to the white matter. It conveys efferent impulses from the cells of Purkinje. Around the body and dendron of each cell of Purkinje is a double basket-work formed by the synapses of the fibres from the star-shaped cells of the outer molecular layer, and from the tendril fibres which arrive from the white matter.

3. **The Nuclear Layer**, or **Inner Molecular Layer**, or **Granular Layer.**—This contains small star-shaped cells, which give rise to axons which reach the outer molecular layer. It also contains irregular Golgi cells, which give rise to an axon which forms synapses with the processes of the moss-fibres of Cajal. Neuroglial cells are also present.

The subjacent white matter contains at least three kinds of nerve fibres :—

Two Sets of Afferent Fibres.—(1) *Moss-fibres of Cajal*, which break up in the nuclear layer. (2) *Tendril-fibres*, which help to form the double basket-work around the cells of Purkinje.

One Set of Efferent Fibres, which are the *axons of the Purkinje cells.*

THE FUNCTIONS OF THE CEREBELLUM.

The cerebellum receives afferent impulses or impressions from various regions of the body; these impressions it appears to "work over," and, as a result of them, originates controlling impulses which appear to govern two sets of nerve cells: (1) the cells of the motor area of the opposite half of the cerebral cortex which originate motor impulses, and (2) the cells of the nuclei of the cranial nerves which are motor in function, and the anterior cornual cells of the spinal cord of the same side.

The Afferent Impulses to the Cerebellum, or cerebellar impressions, are of three types, as follows :—

1. *Kinæsthetic Impressions* (*including tactile impressions*) which arrive from the leg, arm, muscles of the eye, and from other muscles innervated by the cranial nerves. The kinæsthetic impressions from the extremities appear to travel

through two sets of neurones,—the posterior root neurones, which extend from the muscles to the grey matter of the spinal cord, and the ascending spino-cerebellar neurone, which extends from the cells in Clarke's column to the vermis (through the dorsal and ventral cerebellar tracts). These kinæsthetic impressions gain the cerebellum by way of the inferior, middle, and superior cerebellar peduncles.

2. *Visual impressions which come from the retinæ.*—These, in all probability, reach the cerebellum by way of the optic thalami and the superior cerebellar peduncles.

3. *Labyrinthine impressions from the cristæ of the ampullæ of the three semicircular canals*, and also from the *maculæ of the saccule and utricle*, which travel to the vestibular nucleus, thence to the nucleus of Deiters, and from it by way of the middle cerebellar peduncle, and in the internal restiform body through the inferior cerebellar peduncle to the vermis of the cerebellum.

The Controlling Impulses of the Cerebellum. — The cerebellum originates controlling impulses by reason of the motor centres which are present on the cerebellar cortex. The right half of the cerebellum and the right half of the vermis contain motor centres which govern the movements of the right half of the body; the left half of the cerebellum and the left half of the vermis govern the movements of the left half of the body. This fact may be demonstrated by direct stimulation of the cerebellar cortex. If the right half of the cerebellum is stimulated, movements occur on the right half of the body, and the head is rotated towards the *left*, *i.e.* away from the source of irritation. This motor function is exercised *indirectly* through the superior cerebellar peduncles and the contra-lateral cortex cerebri, because, if the opposite half of the cerebral cortex is excised, direct excitation of the cerebellum produces no movement whatever. If the right half of the cerebellum is removed the head becomes turned towards the side of the lesion, *i.e.* to the right; inco-ordinate movements occur in the arm and leg of the right side, and nystagmus follows, owing to the loss of the influence of the cerebellum through the nucleus of Deiters over the ocular nuclei.

It is concluded, then, that the cerebellum controls the opposite motor area of the cerebral cortex, and also the nuclei of the cranial nerves, and the anterior cornual cells of the spinal cord of the same side. This control is represented in the following diagram (Fig. 85).

The result of this cerebellar control over the motor region of the opposite half of the cerebral cortex is that muscular movements are carried out in an orderly manner, *i.e.* the cerebellum is the *highest coordinating centre* of muscular movements. One of the results of the coordination of muscular movements is that the human body is maintained in the upright position, and may also be maintained in other positions if need be, *i.e. equilibration* is maintained.

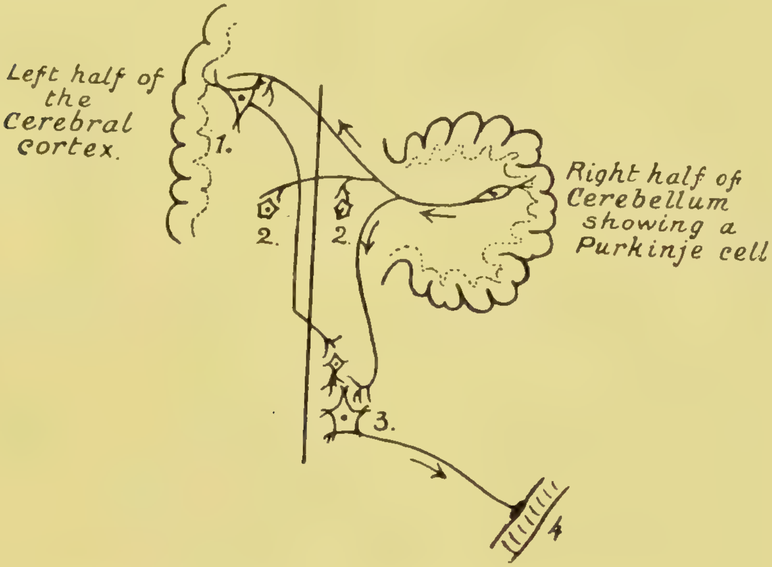

Left half of the Cerebral cortex.
1.
2.
2.
Right half of Cerebellum showing a Purkinje cell
3.
4

FIG. 85.—Diagram to represent cerebellar control.

1.=Pyramidal cell in motor area of cerebral cortex.
2.=Cells of the nuclei of the cranial nerves in the mid-brain, pons, and medulla.
3.=Anterior cornual cell in the spinal cord.
4.=Muscle fibre containing a motor-end organ.

It is found that, if the vermis is stimulated in the middle line, bilateral movements of the animal are produced. If the anterior end of the vermis is stimulated, the animal rotates backwards; if the anterior end is destroyed, the animal falls forward. On the other hand, if the posterior end of the vermis is stimulated, the animal rotates forward; while, if the posterior end is destroyed, the animal rotates backwards.

Ataxia.—It has been pointed out that, in normal circumstances, the cerebellum receives impressions from the muscles, tendons, ligaments, synovial membranes of the joints and skin (kinæsthetic impressions). Those impressions which arrive from the joints are much more important than those from the skin. It also receives impressions from the retinæ and the membranous labyrinths. If these impressions are rendered abnormal, or are in any way interfered with, some form of ataxia or inco-ordination of muscular movement may be brought about.

Spinal ataxia is present when degeneration, followed by sclerosis, occurs in the columns of Goll and of Burdach. This is the result of disease of the posterior nerve root ganglion cells, and as a consequence afferent impulses from the muscles and joints are cut off (locomotor ataxia). If this ataxia, or inco-ordination, is only slight it may be rendered more obvious by depriving the patient of his visual impressions by making him close his eyes when standing upright. Ocular ataxia may follow as the result of the sudden production of squint, or looking down from a great height, conditions both of which cause abnormal visual impressions to travel to the cerebellum.

Spinal ataxia may be partly overcome by keeping the eyes open. In cases of tabes dorsalis the ataxia at once becomes evident when the patient stands with the feet together and then closes his eyes (Romberg's sign).

Aural vertigo, or labyrinthine ataxia, may be produced by experimentally damaging the semicircular canals. This may be readily done in pigeons, but it also occurs as the result of abnormal impressions conveyed to the cerebellum, the result of disease of the labyrinth (Menière's symptoms).

Cerebellar ataxia may occur as the result of poisons acting upon the nerve cells of the cerebellum. If these cells are under the influence of alcohol a characteristic alcoholic (ataxic) gait results. A cerebellar tumour, which encroaches upon the vermis, produces a definite cerebellar ataxia. In cases of cerebellar disease the patient reels or staggers along, and is particularly unsteady when turning round (the cerebellar gait). Another factor in cerebellar ataxia is the existence of muscular hypotonia, which is frequently met with in cerebellar disease; this hypotonia, in unilateral cerebellar lesions, is more defined in the limbs of the affected side. A third important factor in cerebellar ataxia is the want of the co-ordinating influence of the cerebellum on the cerebral motor cortex. This connection is a crossed one, the right half of the cerebellum being connected with the left half of the cerebral cortex, viâ the right superior cerebellar peduncle, and with the spinal cord of the same (right) side, directly by the right vestibulo-spinal tract, and indirectly through the opposite (left) red nucleus. The left red or tegmental nucleus is connected with the anterior cornual cells of the right side of the spinal cord by means of the right pre-pyramidal or rubrospinal tract. "True cerebellar ataxia, unlike the ataxia of tabes dorsalis, is uninfluenced by closure of the eyes" (Purves Stewart).

CHAPTER XLV.

THE AUTONOMIC NERVOUS SYSTEM.

By the autonomic nervous system is meant that portion of the nervous system which appears to be self-governing, and independent of the control of nervous impulses which arise in the cells of the cerebral cortex.

The nerve cells, which constitute the centres of the autonomic nervous system, originate the various nervous impulses which travel to the peripheral organs, such as the blood vessels, walls of the intestines, sweat glands, etc. The fibres which convey these impulses constitute the *efferent* portion of the system. These central nerve cells are, however, to some extent influenced by impulses which reach them from the periphery. The fibres which convey these impulses constitute the *afferent* portion of the system.

THE EFFERENT FIBRES OF THE AUTONOMIC NERVOUS SYSTEM.

For the most part the unstriped muscle (involuntary muscle) of the body is under the control of the autonomic nervous system. As examples of the organs of the body innervated by this system, the following may be mentioned :—

The Heart (cardio-inhibitory and cardio-accelerator nerves).

The Blood Vessels (vaso-constrictor and vaso-dilator nerves).

The Stomach and Intestines (viscero-motor and viscero-inhibitory nerves).

The Secreting Glands, especially the gastric glands, pancreas, and liver (secreto-excitor and secreto-inhibitory nerves).

The Iris (pupillo-contractor and pupillo-dilator).

The nervous impulses, which govern these various organs of the body, arise in nerve cells situated somewhere in the central nervous system. These autonomic nerve centres are situated in the mid-brain, in the pons Varolii, in the medulla oblongata, and in the grey matter of the spinal cord. The efferent impulses leave the central nervous system by finely medullated nerve fibres, some of which travel in the cranial nerves and others in the anterior nerve roots of the spinal nerves. For the most part those nerves which convey the autonomic nerve impulses sooner or later travel to a ganglion, where the medullated nerve fibre or preganglionic fibre arborises around one or more nerve cells in this cell station. New fibres arise in these ganglion cells which are non-medullated (post-ganglionic fibres). If these post-ganglionic fibres pass back to the neighbouring spinal nerve they are termed grey rami communicantes. These fibres convey impulses to the blood vessels (vaso-constrictor), to the sweat glands, and to the hairs of the part (pilo-motor) which is supplied through that particular spinal nerve.

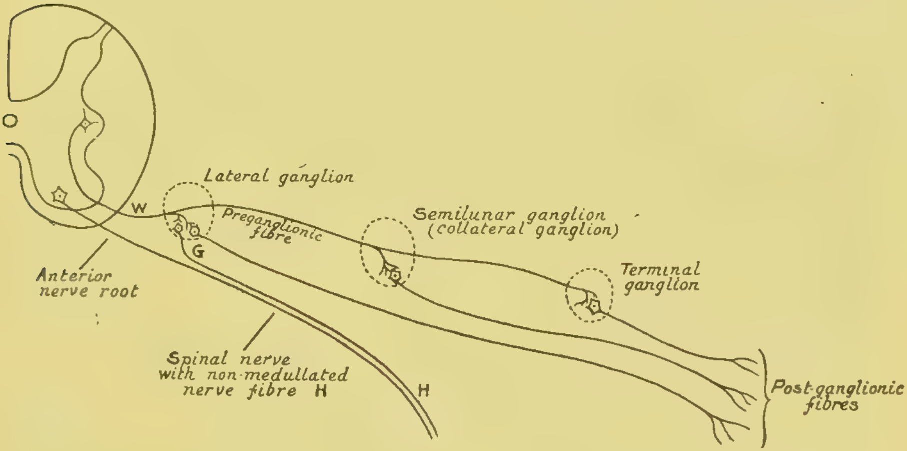


FIG. 86.—Diagram showing some of the cell stations of the autonomic nervous system.

W. = White ramus communicans.
G. = Grey ramus communicans.
H. = Non-medullated nerve fibre.

The nerves conveying the autonomic impulses may make cell stations in one of three regions,—in the proximal lateral ganglia, which form the sympathetic nerve chain; in the more distantly placed ganglia, such as the semilunar ganglia which lie upon the large arteries in the abdomen; or in the terminal ganglia, such as are present in the walls of the viscera, namely, those in Meissner's and Auerbach's plexuses which are present in the walls of the stomach and intestine, and the ganglia present in the walls of the heart.

The positions of the cell stations upon the autonomic nervous system have been demonstrated by Langley's nicotine method. If a preganglionic nerve is stimulated electrically, the impulses which are produced travel through the ganglion to the peripheral nerves which leave the ganglion, with the result that contraction of the plain muscle supplied by the nerves occurs.

If the ganglion is painted with a weak solution of nicotine the nervous impulses are blocked. This is due to the poisonous effect of the nicotine upon the synapses, and also upon the nerve cells themselves, the result of which is to prevent the cells transmitting nervous impulses. If, however, in these circumstances, the post-ganglionic fibres are stimulated, the contraction of the plain muscle in the organ supplied by the nerves may be observed.

The first effect of the nicotine is to excite the nerve cells of the ganglion for a short time only. This is quickly followed by paralysis of the nerve cells, and a blocking of the nervous impulses.

There appear to be four regions in which nerve cells belonging to the autonomic nervous system are grouped together, and which are as follows:—

1. **The Grey Matter of the Central Nervous System.**

(*a*) In the mid-brain there are cells which give rise to fibres which leave by the third cranial nerve. The preganglionic fibres pass to, and make cell stations in, the ciliary ganglion; the post-ganglionic fibres pass out in the short ciliary nerves which supply the sphincter pupillæ, and the two sets of fibres of the ciliary muscle in the ciliary body.

In the region of the third nerve nucleus there are, in all probability, cells which form a centre for the dilator pupillæ, the impulses pass down the cervical region of the cord and leave by the white rami communicantes in the upper thoracic region. The pre-ganglionic fibres appear to travel to the superior cervical ganglion where the cell station is situated. The post-ganglionic fibres travel upwards from this ganglion in the carotid plexus of sympathetic nerves.

(*b*) In the pons and medulla there are probably groups of nerve cells which give rise to various impulses, which leave the region either by some of the cranial nerves or by the spinal cord itself.

The fifth and seventh nerve nuclei contain cells which transmit impulses to the lachrymal gland and the secreting glands in the nose. The ganglion connected with the second division of the fifth nerve is the spheno-palatine, or Meckel's ganglion, and it is connected with the facial nerve through the Vidian nerve.

The glosso-pharyngeal nucleus contains cells which give rise to fibres which leave by the glosso-pharyngeal nerve, and make cell stations in collateral ganglia; these nerves are associated with the secretion of saliva. The cell station for the parotid gland is possibly in the otic ganglion, that for the sublingual gland in the submaxillary ganglion, and that for the submaxillary gland in Langley's ganglion.

The vagus nucleus seems to contain cells which, within limits, are associated with the activity of the digestive secretions, the gastric glands, the pancreas, the liver, and the intestinal glands. The vagus also conveys impulses to the plain muscle of the intestinal walls. The influence of these impulses is to increase peristaltic movements.

The nucleus accessory (spinal accessory) to the vagus nucleus is associated with cells which originate impulses which are cardio-inhibitory in function. The cell stations for these fibres are in the heart itself. Some of the fibres in the vagus probably have cell stations in the ganglia on the trunk of the nerves.

In the medulla there are no doubt special groups of nerve cells, which give rise to nerve fibres which convey nervous impulses down through the cord. The chief *sweat centre* is located in the medulla, and the sweat impulses for the body generally pass away down the cord, though in all probability some pass into the complex fifth nerve nucleus, and so, through the three divisions of that nerve, arrive upon the forehead and face.

The cardio-accelerator centre is most probably present in the medulla, and its impulses travel down the spinal cord, eventually leaving by the anterior nerve roots of the upper thoracic segments of the cord.

The cells of the vaso-constrictor and vaso-dilator portions of the vaso-motor centre are situated in the medulla, and the fibres from them travel away in the antero-lateral descending tract of the spinal cord.

The autonomic centre, which presides over the glycogenic function of the liver cells, is also situated in the medulla oblongata. The efferent impulses travel down the spinal cord, and leave by the white rami communicantes in the upper thoracic anterior nerve roots (*vide* p. 122).

(*c*) In the grey matter of the spinal cord there are nerve cells, which, in most cases, are cells stations for fibres reaching them from the medulla, and which act as subsidiary centres to the higher controlling centres.

There is a cell station for the dilator pupillæ fibres in the grey matter of the lower cervical region. There are subsidiary sweat centres in the grey matter of the lower cervical and upper lumbar regions. There are subsidiary vaso-motor centres in the lateral grey horn all along the dorsal region of the spinal cord, and there are probably cell stations constituting centres for the erection of the hairs (pilo-motor nerves which supply the erector pili muscles). The various efferent impulses leave the cord by the white rami communicantes, or pre-ganglionic fibres, which travel in the anterior nerve roots.

In the lumbar region of the cord there are centres which preside over the movements of the descending colon, the rectum, and the anus. Others situated in this region govern the detrusor and sphincter muscles of the bladder and the erection of the penis (*vide* pp. 446, 720). The majority of these impulses eventually arrive at the peripheral organs by the nervi erigentes.

2. **The Chain of Vertebral** or **Lateral Ganglia** constituting the sympathetic nerve chain.

These are connected with the spinal nerves by the finely medullated nerve fibres which arise in small multipolar nerve cells situated in the anterior cornua of the spinal cord. These fibres leave the cord in the anterior nerve roots, and travel, as the white rami communicantes, to the vertebral or lateral ganglia.

In the thoracic region there are ten or eleven pairs of sympathetic ganglia; in the lumbar region there are usually four pairs of sympathetic ganglia. All the thoracic and the upper two lumbar ganglia are connected with the corresponding spinal nerves by white rami communicantes. For the most part, therefore, the autonomic impulses for the body generally leave the spinal cord between the first thoracic and second lumbar segment.

The impulses for the neck and head travel up through the first thoracic or stellate ganglion, thence through the nerve fibres which encircle the first part of the subclavian artery forming the annulus of Vieussens. They then traverse the inferior, middle, and superior cervical ganglia. The superior cervical ganglion is placed near the base of the skull. It gives rise to fibres which form a plexus of nerves upon the internal carotid artery, and, in this way, the various impulses of the autonomic nervous system get into the skull, and subsequently traverse certain cranial nerves.

The autonomic impulses for the pelvic viscera travel down through the lower two lumbar ganglia to the four ganglia of the sacral part of the ganglionated cord. Other autonomic impulses for the pelvic viscera travel in the pelvic splanchnic nerve, which is made up of branches from the second, third, and fourth sacral nerves without being in direct communication with the ganglionated nerve chain. The three last-mentioned nerves are regarded as the homologues of the white rami communicantes of the thoracic and upper two lumbar nerves.

The two sympathetic chains are connected below by the ganglion impar or coccygeal ganglion which lies in front of the coccyx.

In the lateral chain of ganglia are the cell stations for the vaso-constrictor fibres of the trunk and limbs. The cell stations for the vaso-constrictor fibres for the head are in the superior cervical ganglion. In the lateral chain of ganglia there are also cell stations for the sweat and pilo-motor nerves.

3. **The Intermediate,** or **Collateral Ganglia.**—These include the ciliary, spheno-palatine or Meckel's ganglion, the otic, submaxillary, and Langley's ganglion, also the semilunar, superior mesenteric, and inferior mesenteric ganglia.

The semilunar ganglia give rise to the cœliac plexus of nerves. The superior and inferior mesenteric ganglia give rise to the hypogastric nerves which join the pelvic plexus. The nervi erigentes of this plexus supply vaso-dilator fibres to the penis, clitoris, rectum, and anus, and motor fibres to the muscle walls of the pelvic colon and rectum. The cell stations for the nervi erigentes are in the terminal ganglia, which are situated in the walls of the viscera to which they are distributed.

4. **The Terminal** or **Distal Ganglia.**—These are placed in the organs; they include the ganglia of Remak, Bezold, and

Bidder in the heart, the peripheral ganglia found along the course of the blood vessels, and the plexuses of Auerbach and Meissner, located in the wall of the stomach and intestines.

The nerves of the autonomic nervous system may be classified as follows :—

ANABOLIC.	**KATABOLIC.**
(With cell stations in the collateral or in the terminal ganglia.)	(With cell stations in the lateral or in the collateral ganglia.)
Cardio-inhibitory.	Cardio-accelerator.
Vaso-dilator.	Vaso-constrictor.
Viscero-inhibitory.	Viscero-accelerator.
Secreto-inhibitory.	Secreto-excitor.

The complexity of the fibres which convey efferent autonomic impulses up the cervical sympathetic nerve chain may be gathered by noting the changes which follow section of this nerve, and also those which follow the electrical stimulation (faradisation) of the upper or oral cut end of the nerve. The phenomena which follow section of the sympathetic nerve in the neck are as follows :—

1. The arterioles supplied by the divided vaso-motor nerves dilate. If the nerve is divided in the neck of a white-eared rabbit, capillaries in the rabbit's ear which were previously quite small become flushed with arterial blood and can be seen quite readily.

2. The upper lid droops slightly (partial ptosis). This is due to loss of tone of the plain muscle of Müller in the upper lid, which is innervated by the sympathetic.

3. The eye-ball recedes to a very slight degree. This is due to the fact that the plain muscle of the capsule of Tenon is paralysed. At the same time the orbitalis muscle, which in some animals stretches across the spheno-maxillary fissure, is also paralysed. This phenomenon of retraction of the eyeball is called enophthalmos, and occurs when the sympathetic nerve in the neck becomes paralysed.

4. The pupil becomes contracted, due to paralysis of the dilated pupillæ muscle, which is supplied through the sympathetic nerve. The sphincter pupillæ, innervated through the third cranial nerve, contracts unopposed.

The phenomena which follow stimulation of the upper or oral cut end of the cervical sympathetic nerve are—

1. The cutaneous arterioles supplied through the nerve become constricted, and consequently the parts supplied by these blood vessels become pale.

2. In some animals sweating occurs in the parts supplied through the sympathetic nerve; in dogs the hairs become somewhat erected, because the sympathetic nerve supplies the pilo-motor muscles.

3. There is an increased flow of saliva, which is thick and viscid ("sympathetic saliva").

4. The eye phenomena are as follows:—

The palpebral fissure becomes wider because of the retraction of the upper lid (Müller's muscle). The eyeball becomes slightly protruded (exophthalmos); this is due to the contraction of the unstriped muscle in Tenon's capsule. The pupil becomes dilated, because the dilator pupillæ is supplied through the sympathetic, and also because the arterioles in the iris become constricted.

THE AFFERENT FIBRES OF THE AUTONOMIC NERVOUS SYSTEM.

The white rami communicantes, which are the visceral branches of the spinal nerves, take origin by two roots, from the anterior and posterior roots of the spinal nerves. The majority of the fibres, however, are from the anterior nerve roots, and these are efferent in function. The fibres of the white rami communicantes, which arise from the posterior root, are axons of some of the cells in the posterior root ganglion. These fibres make no cell stations in the vertebral, collateral, or distal ganglia. They are *afferent* in function, and contain amongst others the "sensory" fibres of the viscera. If a mixed nerve, such as the sciatic, is cut, and its upper cut end is faradised, certain phenomena follow, but amongst these there is a reflex rise of arterial blood pressure (pressor effect) due to reflex contraction of the plain muscle in the walls of the peripheral arterioles of the splanchnic area. A similar effect may be produced by stimulating the central cut end of the white rami communicantes. The depressor nerve is another example of a nerve of the autonomic system which conveys afferent impulses. If the upper cut end of this nerve is stimulated, there follows a reflex vaso-dilatation of the peripheral arterioles of the splanchnic area, and the arterial blood pressure gradually falls. If the upper cut end of the great sciatic nerve, or the vagus, or the depressor nerve is stimulated, there follows, amongst other phenomena, an increased formation of dextrose from the glycogen which has been previously stored in the liver cells (*vide* p. 122).

CHAPTER XLVI.

TROPHIC NERVES.

There is no evidence that there are separate nerves which convey efferent impulses governing the nutrition of the organs and tissues of the body. In all probability, however, the anterior cornual cells of the spinal cord, and the analogous cells constituting the nuclei of the "motor" cranial nerves, not only control the metabolism, and consequently the nutrition of the nerve fibres which arise from them (*vide* "Wallerian Degeneration"), but also appear to exercise a nutritional or trophic influence upon the muscles to which they are distributed. If a motor nerve is divided, not only does the peripheral portion, which originally grew away from the nerve cells of the anterior cornua of the cord, undergo acute or rapid Wallerian degeneration, but the muscle fibres to which the nerve is distributed become quickly changed. The change is so rapid that it cannot be explained upon the simple theory of disuse (disuse atrophy). In the disease called acute anterior poliomyelitis, or infantile paralysis, there is thrombosis, or blood clotting, in the blood vessels which supply the anterior cornua of the spinal cord. This is followed by destruction of the anterior cornual cells in either the cervical or lumbar enlargements, succeeded by rapid degeneration of the efferent nerve fibres which arise from these cells, and rapid atrophy of the muscles of the limb supplied by the nerves.

In cases of injury to the spinal cord, such as may be produced by fracture-dislocation of the spine, accompanied by bruising or rupture of the spinal cord and consequent damage of the anterior cornual cells, bed sores form very rapidly (acute bed sores), which are local ulcers due to trophic disturbances commencing in the skin.

It is concluded, therefore, that the cells which give rise to and preside over the metabolism and nutrition of motor nerves also preside over the metabolism and nutrition (within certain limits only, because to a considerable extent the tissues govern their own oxidative changes) of the muscles supplied by them. When these metabolic influences are interfered with, *e.g.*, when a motor nerve is severed, trophic changes take place in the tissue supplied by the nerve, and rapid *atrophy* consequently ensues.

It must be remembered, however, that vaso-motor nerves traverse the anterior cornua of the spinal cord in the dorsal region, and when these are damaged, vaso-motor changes occur in the tissues which they supply. Some of the more chronic changes which take place in a limb, when its motor nerve is damaged, therefore *may* be of vaso-motor origin.

Trophic disturbances also occur in the tissues when the ganglion cells, situated upon the afferent nerves, are diseased. The nerve cells usually involved are those in the posterior nerve root ganglia of the spinal nerves, and the analogous ganglia of some of the "sensory" cranial nerves, such as the Gasserian ganglion. Trophic disturbances may also occur in an area when the afferent nerve from that area is involved in disease. The following are some examples of trophic disturbances, or atrophic changes, occurring in various parts of the body, resulting from disease of the first afferent neurone; this neurone includes the arborisation in the peripheral "sensory-end-organ," the nerve fibre from the end organ travelling into the central nervous system and the ganglion cell connected with this nerve fibre.

After excision of the Gasserian ganglion, trophic ulcers frequently occur in the cornea, the sensory nerve of which is the first division of the fifth. In some cases of chronic glaucoma, in which disease the tension of the eyeball is so raised that the sensory nerves of the globe, which course along between the sclerotic and choroid coats, are so pressed upon (pressure atrophy) that the cornea becomes anæsthetic, trophic ulcers sometimes occur.

Inflammation of the divisions of the fifth cranial nerve is associated with the trophic disturbance of the skin of the forehead, epithelium of the cornea, and skin of the face, called herpes (herpes frontalis, herpes cornealis, herpes facialis).

If the vagi of an animal are tied, atrophic changes occur in the lungs; these are followed by trophic pneumonia and gangrene. Fatty degeneration of the cardiac muscle of the animal is also found on post-mortem examination.

Inflammation of the intercostal nerves, and possibly also inflammation of the posterior nerve root ganglion cells, is associated with intercostal herpes, or shingles.

Locomotor ataxia (tabes dorsalis) is a disease associated with early degeneration of the posterior nerve root ganglion cells, which usually commences in the lumbar region of the cord, and, in the later stages of the disease, atrophic disturbances of rapid onset frequently occur in the joints, especially of the lower extremity, so that the joints become completely disorganised (Charcot's disease). In some forms of peripheral neuritis, followed by nerve degeneration, trophic ulcers rapidly form on the sole of the foot, and perforate to the dorsum. Such do occur in locomotor ataxia, and in the peripheral neuritis of diabetes mellitus.

These examples will suffice to show that atrophic changes occur as a result of disease of the peripheral afferent neurone. It may be reasonably concluded that the ganglion cell upon this neurone, which originally gives rise to the fibre of the neurone, exercises a trophic influence not only upon the nerve fibre itself, but also upon the cells connected with the peripheral portion of the fibre. It will be remembered that the cells of these root ganglia were originally bipolar; one pole gave off a fibre which grew into the central nervous system, and the other pole gave off a fibre which grew away towards the periphery (*vide* p. 474). The function of the peripheral "sensory" neurone is afferent, *i.e.* in the ordinary way it conveys afferent impulses, but, just as vaso-dilator impulses may be conveyed peripheral-wards (antidromic conduction) along the first afferent neurone (*vide* p. 222), so is it possible that trophic impulses may be antidromal too.

It is only fair, however, to mention that the trophic disturbances which follow disease of the peripheral afferent neurone have been explained also as follows: that the disease of the afferent neurone is followed by local anæsthesia; that, therefore, local injury occurs more readily; and that, when it does, it is followed by ulceration (atrophy). In other words, that the disease of the afferent neurone is the *predisposing* cause, but that the local injury is the *exciting* cause of that destructive inflammation, which is followed by ulceration (atrophic ulcer).

SECTION XII.

NERVE—MUSCLE.

CHAPTER XLVII.

NERVE.

THE muscles, both voluntary and involuntary, are controlled by the central nervous system. The voluntary muscles are innervated by the medullated nerves, the involuntary by the non-medullated nerves. Voluntary muscles may be influenced by afferent nervous impulses which originate in the skin, and the response of muscles to such superficial stimuli is called a reflex movement.

Reflex Movement.—The stimulus arises in a sense organ in the skin, and the nerve impulse travels up an afferent nerve and traverses the posterior nerve root ganglion, where each afferent nerve fibre is connected by a T-shaped junction with a unipolar nerve cell. The fibre then enters the posterior cornu of grey matter, and forms a synapse with small posterior cornual cells. From these cells short axons travel forward to form synapses with the large anterior cornual cells.

The multipolar nerve cell in the anterior horn of the spinal cord, and its long projection fibre which branches, constitute the lower motor neurone. Each fibre finally branches in the muscle, and each branch ends in a motor end organ, which is situated within the sarcolemma sheath of the transversely striated muscle fibre.

Voluntary Action.—In this case the nervous impulse arises in the large pyramidal nerve cells, or cells of Betz, which are present in the motor area of the cerebral cortex. The impulse so originated travels down the upper motor neurone through the corona radiata, thence to the internal capsule of the corpus striatum, and through the crusta of the mid-brain. The impulse then arrives at the pons Varolii, and, should the voluntary action take place in the face, the impulse travels across the middle line in the pons to the facial nucleus of the opposite side. If, however, the voluntary action occurs in the extremities, the impulse travels directly through the pons and medulla. The fibres of the upper motor neurone, for the most part, cross at the decussation of the pyramid, and travel down in the crossed pyramidal tract in the opposite side of the spinal cord. The upper motor neurone ends by forming synapses with two or more nerve cells situated at the base of the posterior cornu of the cord. These posterior cornual cells give rise to short axons, which convey the impulses forward to the large anterior cornual multipolar nerve cells. Here one small neurone from a posterior cornual cell forms synapses with two or more multipolar nerve cells. The lower motor neurone takes the nervous impulses through its various branches to the motor end organs which are present in the voluntary muscle fibres. It is by means of synapses at the base of the posterior cornua, and those in the anterior cornua, and the branches of the medullated nerve fibres, that each pyramidal cell of Betz is able to influence many muscle fibres (*vide* Fig. 81).

The Nature of Nerve Impulses.

From the physico-chemical standpoint the phenomena of electric currents in nerve are due to the movements of ions which carry charges of electricity. Currents of injury, currents of action (negative variation), and electrotonic currents, which are described later, are all explained in this way. The electrolyte, which appears to be most abundant in nerve fibres, is KCl. By treating fresh nerves with cobalt sodium hexanitrite (a precipitate) is produced where potassium is present. The excess of the reagent is washed away with ice-cold water, and the precipitate in the nerve fibres is then blackened with ammonium sulphide. Macallum found a precipitate in the medullary sheath and at the nodes of Ranvier, but none in the axis cylinder. Chlorides are detected by treating the fresh nerves with a solution of $AgNO_3$, which contains a little HNO_3. Chlorides are found all along the axis cylinder process.

Macallum's researches tend to show that chlorides are present in the active part of a nerve (the axis cylinder), while potassium is more abundant in the protecting medullary sheath. These dissolved electrolytes appear to be the causes of electric currents, and therefore, *presumably*, of nervous impulses; but as to how these electrolytes act is quite an open question.

The Direction of a Nerve Impulse.

Under normal conditions, nerve impulses pass down motor nerves (centrifugal impulses) and up "sensory" nerves (centripetal impulses), but both varieties of nerves may transmit impulses in either direction. Nerve cells, however, will not allow nerve impulses to traverse them in a contrary direction.

Langley has shown, by dividing the vagus nerve in the neck and suturing the central cut end to the oral cut end of the cervical sympathetic, which had been previously divided between the superior and middle cervical ganglia, that stimulation of that part of the vagus nerve, sutured to the sympathetic, causes nerve impulses to travel along that nerve to the cervical sympathetic, which result in constriction of the blood vessels of the face and dilatation of the pupil of the same side. This experiment demonstrates that the molecular changes, which occur in a nerve as the result of stimulation, produce the same ultimate result, although the impulses have reached their destination by an unusual channel. In cases of facial nerve paralysis, Ballance performed similar surgical experiments. He has sutured part of the spinal accessory nerve to the peripheral refreshed end of the facial nerve. In his most successful case the patient recovered the use of the paralysed facial muscles (N. H. Alcock).

The Velocity of a Nerve Impulse.

This is measured, in a cold-blooded animal like the frog, by making a nerve-muscle preparation with a long piece of nerve, and stimulating the nerve at two points by a single induction shock, and observing the difference of time in the two responses (*vide* Fig. 87).

The nerve is first stimulated at A, and the muscle contracts; this response is recorded on a rapidly moving surface. The nerve is then stimulated at B, again the muscle contracts; this too is recorded. The difference in time between the two responses may be measured, and indicates the time that the nerve impulse took to travel from B to A. In the frog, at room temperature, the velocity of a nerve impulse is about 27 metres per second.

In man the velocity of a nerve impulse in a motor nerve may be measured by holding the transmission myograph between the thumb and fingers. One rheophore is placed upon the thenar eminence, and the other first upon the moistened skin over the median nerve at the bend of the elbow, then upon the moistened skin over the cords of the brachial plexus directly below the clavicle. The difference in time between the two responses indicates the time it takes for the nerve impulse to travel through a length of nerve from below the clavicle to the bend of the elbow. A similar experiment may be performed upon "sensory" nerves. A man replies to a stimulus such as an induction shock applied to his toes, and then replies to a second stimulus applied to his knee. The time interval between the two responses may be readily measured.

In man the velocity of a nerve impulse, both for motor and "sensory" nerves, is about 66 metres per second. The velocity of nerve impulses along non-medullated nerves appears to be much slower.

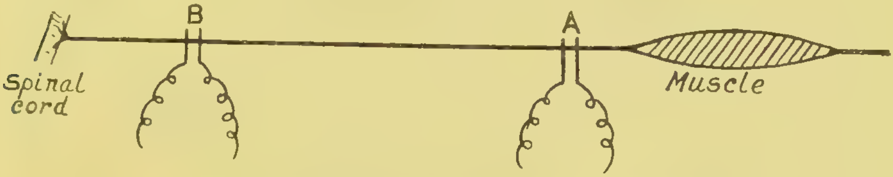


FIG. 87.—Diagram of a nerve-muscle preparation.

Electric Phenomena of Nerve.

An excised medullated nerve, such as the sciatic nerve of the frog, may be kept in a surviving condition for a time by bathing it with an isotonic solution of sodium chloride to which has been added a small quantity of dextrose. Such a nerve appears to be very much in the same electric condition as it was in the body, namely, *isoelectric*,—that is, if the nerve is tested with a galvanometer it gives no indication of any current.

Such a nerve will show three varieties of electric phenomena :—

1. A current of injury.
2. The current of action or negative variation.
3. Electrotonic currents.

1. **Current of Injury.**—If an injury is made at any point in an isoelectric nerve, that spot becomes electrically negative (zincative) to the uninjured part, and this difference of potential gives rise to the current of injury (N. H. Alcock)

The direction of the current will be readily understood from the following diagrams :—

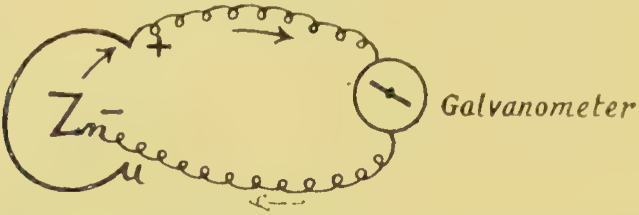


FIG. 88.—Diagram representing a Daniell cell, showing the current flowing from the zinc to the copper *in* the cell, and from copper to zinc *outside* the cell.

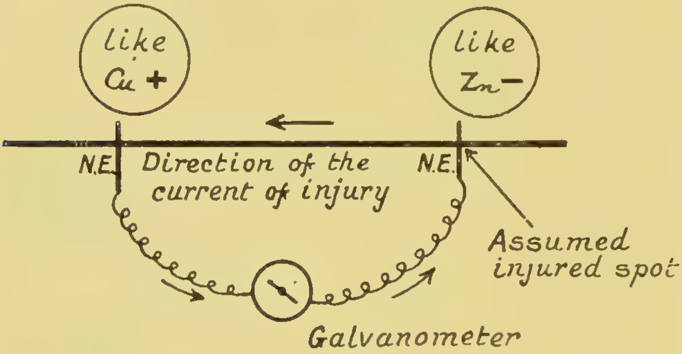


FIG. 89.—Diagram of "injured nerve." N.E. = Non-polarisable electrodes.

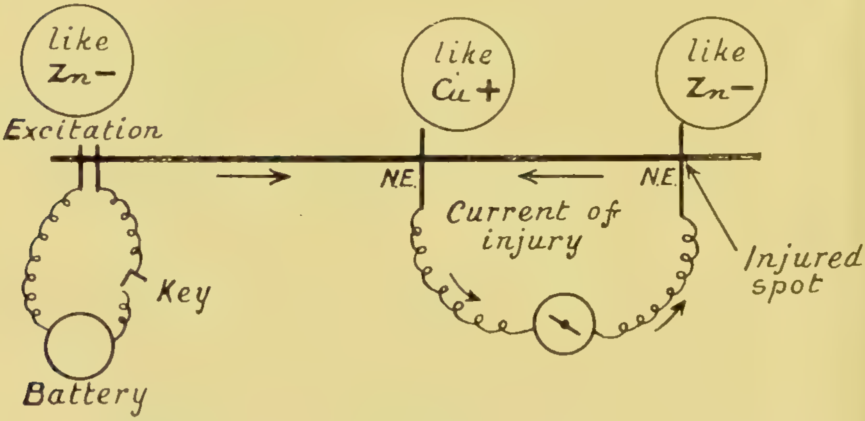


FIG. 90.—"Negative variation" of the current of injury. N.E. = Non-polarisable electrodes.

If a medullated nerve which has been injured is stimulated, the *uninjured* and stimulated portion becomes electrically negative (zincative), so that currents arise which flow in the opposite direction to the currents of injury. The result is that the currents of injury appear to become diminished; that is, there is a diminution or "negative variation" of the current of injury. This will be understood from Fig. 90.

If an uninjured nerve is excited, a wave of zincativity passes along it, each point becoming successively electrically negative or zincative to the rest; this is termed the current of action. From this it will be seen that (1) an injured spot is electrically negative (zincative) to an uninjured spot, and (2) an active spot is electrically negative (zincative) to an inactive spot (N. H. Alcock).

2. **The Current of Action**, or "**Negative Variation**," has been observed in nerves which are conducting impulses in a natural manner without any extraneous excitation. The nerves upon which observations have been made are the phrenic and the vagus, because these nerves conduct impulses which recur with each act of respiration. In experimenting upon the vagus, Lewandowsky, by using the galvanometer, demonstrated that a current of action (negative variation) occurred each time the lungs were artificially expanded (positive ventilation). By using the capillary electrometer Alcock and Seemann observed the same phenomenon. They, however, went further, and showed that a current of action occurred at each normal inspiration (indicating that an impulse passes *up* the nerve during this phase), and a current of action was also observed when negative ventilation was performed upon the lungs.

3. **Electrotonic Currents.**—While a constant electrical current is flowing through a nerve three sets of changes occur; these are called electrotonic variations, or electrotonus. The changes are in the *electrical condition*, in the *excitability*, and in the *conductivity* of that nerve.

These will be considered in order.

(1) *Change in Electrical Condition and the Production of Electrotonic Currents.*—In order to demonstrate the production of electrotonic currents a nerve-muscle preparation (uninjured) must be carefully made from a frog, a piece of spinal cord left attached to the sciatic nerve and the muscle preferably *in situ*. No obvious change occurs in the muscle. The preparation is arranged as in Fig. 91, and

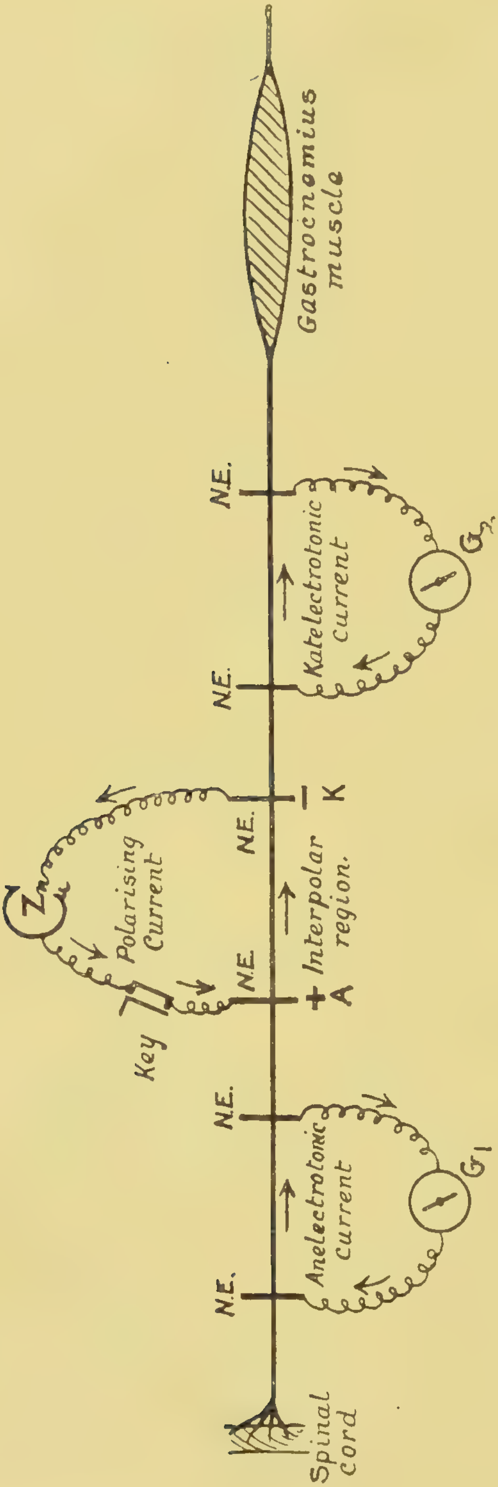


Fig. 91.—"Electrotonic Currents."

N.E. = Non-polarisable electrodes. G_1 and G_2 = Galvanometers.

the nerve muscle kept moist with an isotonic salt solution which contains a little dextrose.

The polarising current is led off from the battery through non-polarisable electrodes to the nerve between A and K,—A represents the anode, and K the kathode. The result of this polarising current is that a current is set up in the nerve in the extra-polar regions. That current which occurs in the extra-polar region near the anode is called the anelectrotonic current; its presence is indicated by the deflection of the needle of the galvanometer G_1, and its direction in the nerve by the arrow, *i.e.* it flows towards the anode. In the extra-polar region near the kathode the katelectrotonic current is produced, its presence is indicated by the deflection of the needle of the galvanometer G_2, and its direction by the arrow, *i.e.* it flows away from the kathode.

These electrotonic currents vary directly in intensity with the strength of the polarising current, and they last while this polarising current passes through the nerve. If the polarising current is removed by raising the key, *after-electrotonic currents* are produced, whose direction is indicated as follows:

Anelectrotonic Region.	Interpolar Region.	Katelectrotonic Region.
→ At first ← later	← If, however, the original current was strong and of short duration →	→ In all circumstances

These currents are dependent upon the physical integrity of medullated nerve; they are not found in non-medullated nerve, muscle, or tendon; they are diminished, or even absent, in degenerated nerve.

"Paradoxical contraction" depends upon the presence of electrotonic currents. This may be shown in the following diagram (Fig. 92).

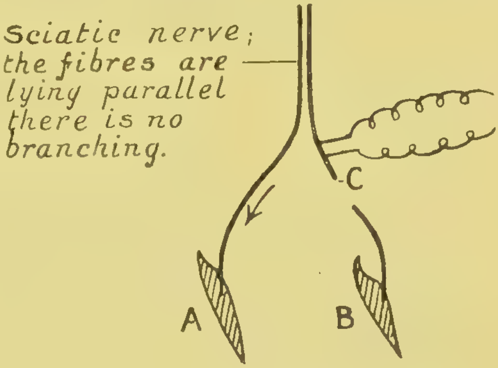

Sciatic nerve; the fibres are lying parallel there is no branching.
C
A
B

Fig. 92.—"Paradoxical Contraction."

In the thigh of a frog the sciatic nerve divides in order to supply different sets of muscles. If one branch is cut and the central cut end is stimulated *electrically* at C, the electro-tonic variations set up in C cause nerve impulses to travel down to A, and the muscles A contract. It should be noted that the spinal cord must be previously destroyed in order to exclude the possibility of reflex movement; the fibres in the sciatic nerve are represented as separate fibres without any branching.

(2) *Change in Excitability.*—When a constant current is passed through a nerve, the excitability of the nerve is increased around the region of the kathode, and diminished

around the region of the anode. The after-effect of the constant current, for a short time only, is the reverse of this; since, when the constant current is broken, there is a diminution of excitability in the region of the original kathode, and an increased excitability in the region of the anode. These changes in excitability may be demonstrated thus—

The apparatus is arranged as follows (*vide* Fig. 93):

The secondary coil is placed away from the primary coil, so that the muscle responds well to a break-shock from the exciting circuit, but does not respond to a make-shock. The response of the muscle to the break-shock may then be recorded. The polarising circuit is then thrown in, or "made," and the direction of the current is so arranged, by the reverser R, that the electrode NE next to the exciting electrodes is the kathode, *i.e.*, the direction of the polarising current is descending. The preparation is then excited by a break-shock from the exciting circuit, the result of which is a greater contraction of the muscle than before, and the nerve muscle preparation may even respond to a make-shock. The increase of irritability of the nerve around the kathode is called katelectrotonus, and usually occurs in nerves when they are in the early stage of inflammation. If, however,

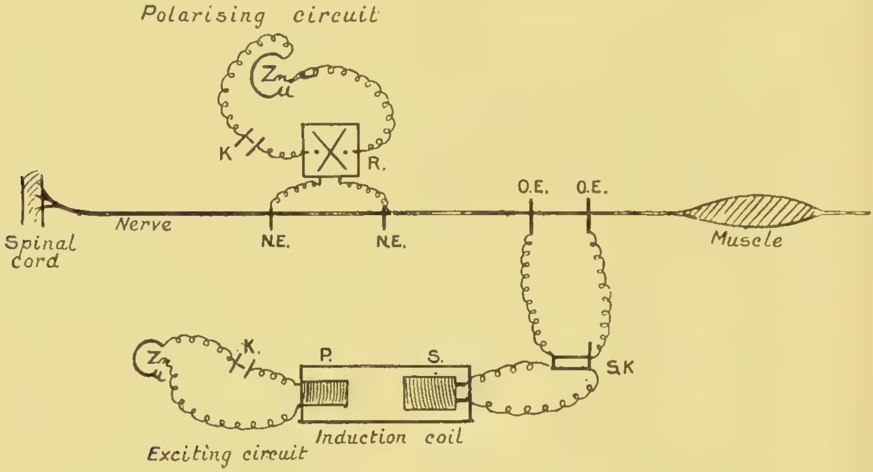


FIG. 93.

K=Make and break key.
S.K=Short circuiting key.
R=Reverser.
N.E=Non-polarisable electrodes.
O.E=Ordinary electrodes.
P=Primary coil.
S=Secondary coil.

the polarising circuit is so arranged that the electrode NE nearest to the exciting electrodes OE is the anode, *i.e.*, the direction of the polarising current is ascending; then, if the preparation is stimulated by breaking the exciting circuit, the contraction of the muscle is small. This diminution of excitability of the nerve around the anode is called anelectrotonus, and is shown in the later stages of inflammation of a nerve when the nerve is becoming destroyed. Similar results may be obtained when the stimuli are either mechanical or chemical as well as electrical. The following diagram represents the alteration of excitability of a nerve when a polarising current is passing through it (*vide* Fig. 94).

It will be seen that the rise in excitability around the kathode gradually shades off into a diminished excitability

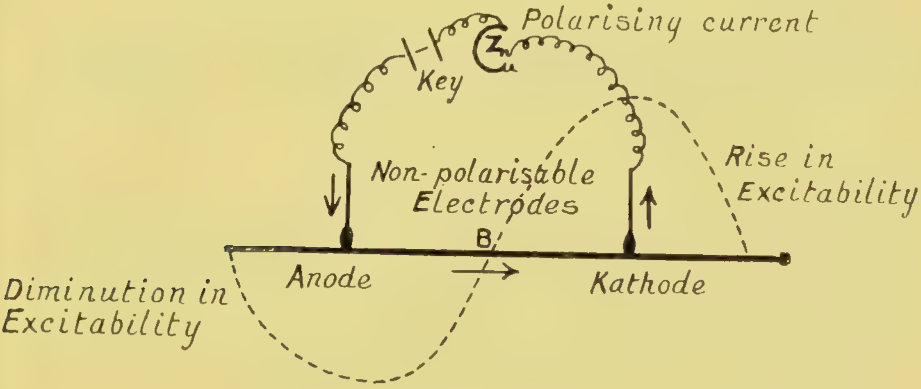


FIG. 94.

around the anode. There must obviously be a *neutral point* B. If the polarising current is weak, this *neutral point* is nearer the anode; if strong, it is nearer the kathode.

(3) *Change in Conductivity.*—It has been shown that when a constant current is passed through a nerve the nerve becomes more excitable around the kathode (katelectrotonus). With this increase of excitability there is increased conductivity. With the diminution of excitability around the anode (anelectrotonus) there is also diminished conductivity. In other words, excitability and conductivity of nerve, as a rule, vary directly with each other.

The following experiment, introduced by Gotch, demonstrates this fact. The preparation is arranged as in Fig. 95.

Key 2 is opened, key 1 is put down and the upper circuit made, the muscle contracts. Key 1 is then opened and key 2 put down, the lower circuit is made and the muscle contracts, but not so quickly as when the upper circuit is made. In each case the kathode is the stimulating electrode at make, and the cause of the delay, when the lower circuit is made, is due to the lowered conductivity of the nerve around the anode$_2$ at make.

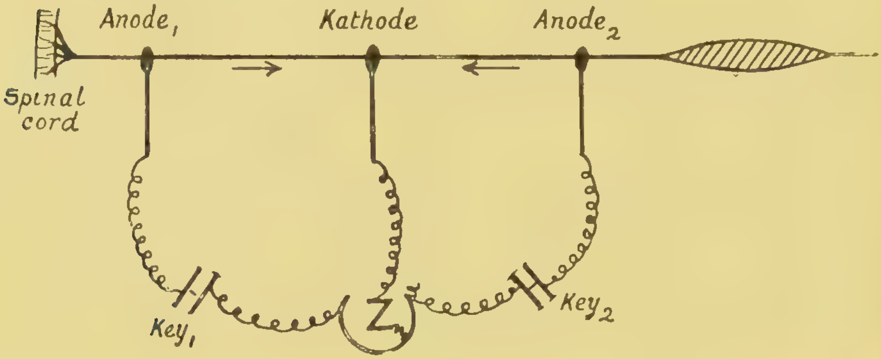


FIG. 95.

THE RELATIONSHIP BETWEEN THE EXCITABILITY AND CONDUCTIVITY OF NERVE.—It has been already stated that the excitability and conductivity of nerve vary directly with one another, but, by using the apparatus described below, and by exposing the nerve of a nerve-muscle preparation to various

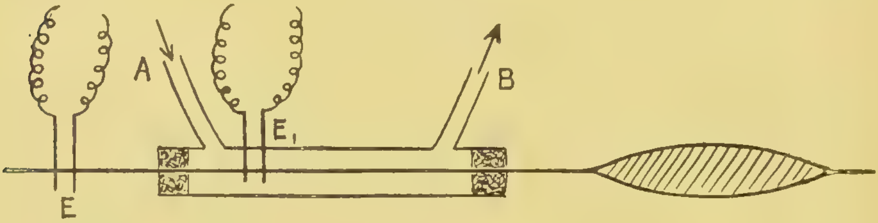


FIG. 96.—Nerve-muscle preparation with nerve lying inside a glass tube, carefully plugged at each end with China clay, made with isotonic salt solution ; the nerve must not be compressed.

E=Electrodes under the nerve outside the glass tube.
E$_1$=Electrodes under the nerve inside the glass tube.
A and B=Side tubes by which gas, etc., may be admitted to the glass tube which contains the nerve.

reagents, it may be shown that, under experimental conditions, excitability and conductivity may be made to vary independently of each other (*vide* Fig. 96).

If a stream of CO_2, ether vapour, or a moderately cooled isotonic salt solution, is passed for a short time through the glass tube which contains the nerve, and the nerve is stimulated through the electrodes E_1, there is no response in the muscle. The nerve is no longer excitable. If the nerve is stimulated by the electrodes E, the muscle will contract, showing that there is no loss of conductivity of the nerve within the tube. If, however, these reagents are allowed to have a prolonged action, the muscle will not contract when the nerve is stimulated at E, showing that conductivity has also disappeared.

The reagents used cause excitability to disappear before the power of conductivity.

If alcohol vapour is used, conductivity is said to disappear before excitability.

When the reagents used are replaced by air the nerve gradually recovers, and as a rule conductivity returns before excitability.

The Stimulating Electrode.

At make, the kathode is the stimulating electrode, and at break, the anode is the stimulating electrode. This may be shown with the apparatus arranged as follows; non-polarisable electrodes are used.

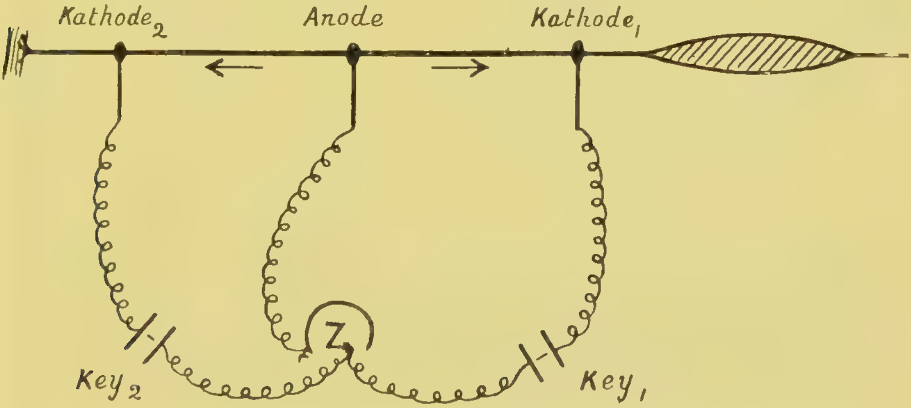


FIG. 97.

Key 2 is raised, key 1 is put down and the lower circuit made, the muscle quickly responds.

Key 1 is now raised and key 2 put down, the muscle takes longer to respond, the stimulus, started at kathode 2, has to travel through a long piece of nerve to the muscle, and also through an area of nerve around the anode in which the conductivity is lowered.

That the kathode is the stimulating electrode at make, and the anode at break, is due to the rise of excitability which occurs, and which in each case acts as the stimulus. That the kathode is the stimulating electrode at make, and the anode the stimulating electrode at break, may also be shown as follows. A long piece of muscle from a frog is clamped at one end, and the lower portion is divided longitudinally. Into each free end a small silver hook is placed, which acts as a non-polarisable electrode; the circuit is arranged with a reverser R (*vide* Fig. 98).

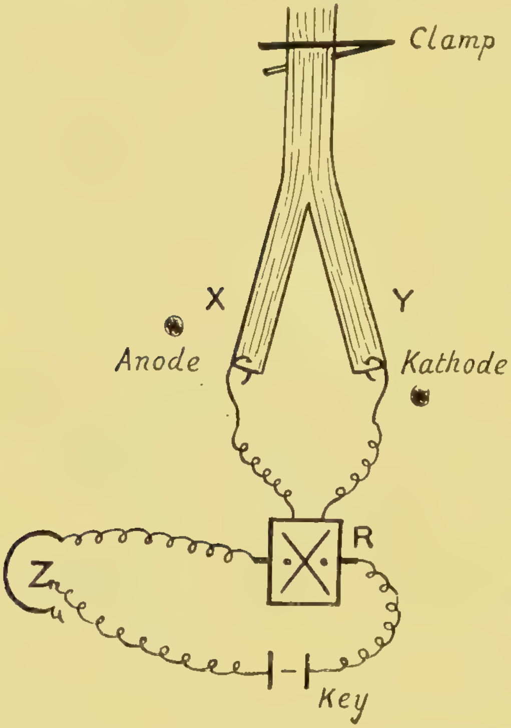


FIG. 98.

If the circuit is made by putting down the key, the piece of muscle Y, to which the kathode is attached, contracts before the piece of muscle X to which the anode is attached. On reversing the direction of the current by which the kathode is attached to X, on making the circuit the piece of muscle X, which has the kathode attached, contracts before the piece of muscle Y which now has the anode attached. In a similar manner it may be shown that, at break, the anode is the stimulating electrode.

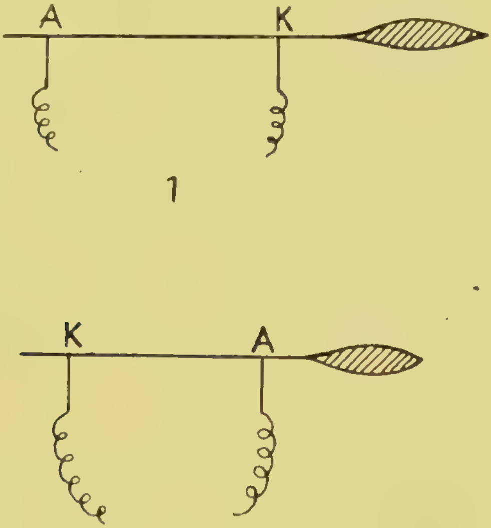
From what has been already stated it will be seen that of the two responses obtained with a make-shock arranged as in Fig. 99, the response of the muscle, as arranged at 1, will be greater than the response obtained with the arrangement as at 2, the strength of the stimulus in each case being equal.

This is due to the fact that, in case 2, with a make-shock, there is *lowered excitability* and *lowered conductivity* around the anode A. There is some resistance to the impulse, therefore, under normal conditions; the kathodal closure contraction is greater than the anodal closure contraction, or the

K.C.C. is > the A.C.C.

In the early stages of nerve degeneration it is found that the reverse holds good, namely—

The A.C.C. is > the K.C.C.



1

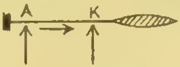
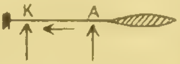
2

FIG. 99.

Pflüger's Law of Contraction.—For the demonstration of this law of contraction the apparatus must be arranged as follows: The cell is connected to the middle binding screws of a reverser, from the terminal screws of which wires are carried to a rheochord, and from the adjacent screws of the rheochord, wires are carried to the non-polarisable electrodes placed under the nerve of a carefully prepared and undamaged nerve-muscle preparation with a piece of spinal cord attached.

The strength of current is regulated by the number of cells used and by the rheochord, and its direction by the reverser.

The contractions C, which occur in the muscle of a nerve-muscle preparation when a constant current is made and broken, vary with the strength and direction of the current, and the results obtained constitute Pflüger's law. These results are as follows:

Strength of current (relative)	*Descending current* 		*Ascending current* 	
	Make	*Break*	*Make*	*Break*
Weak	C	–	C	–
Moderate	C	C	C	C
Strong	C	–	–	C

These results can be readily understood if the foregoing facts are kept in mind, and are—

1. That the condition of a nerve around the kathode is one of increased excitability and increased conductivity, and that when the current is broken the after-effect is the reverse of this.

2. That the condition of a nerve around the anode is one of diminished excitability and conductivity, and that when the current is *broken* the after-effect is the reverse.

3. That the increase and decrease of excitability and of conductivity are more marked about the kathode than they are about the anode.

4. That, at *make*, the kathode is the stimulating electrode, whereas, at *break*, the anode is the stimulating electrode.

Ritter's Tetanus.—If a strong ascending current is passed through a nerve-muscle preparation and the current suddenly broken, the sudden rise of excitability of the nerve around the anode at break is sometimes sufficient to bring about those electrolytic changes produced by the current, which end in tetanus of the muscle. The tetanus may be overcome by *making* the strong ascending current, by means of which there is a sudden fall in excitability around the anode at make. A similar result may occur when suddenly *making* a strong descending current, the rise in excitability of the nerve around the kathode, which is the nearest to the muscle, often ends in tetanus. This may be overcome by breaking the circuit, which causes a sudden fall in excitability of the nerve around the kathode.

Reaction of Nerve Muscle in Man.

Nerve fibres respond most readily to induction shocks, and therefore to the faradic current. When a muscle is stimulated by faradism, the response is obtained by means of the motor end-organs.

In normal circumstances, muscles quickly respond to the make and break of a constant current, but this reaction probably occurs through the motor end-organs.

The kathodal closure contraction, as previously stated, is greater than the anodal closure contraction.

When groups of muscles become paralysed it is important to determine whether the lesion is in the upper or the lower motor neurone.

If the upper motor neurone is at fault the paralysed muscles undergo slight wasting from disuse, but they do not give the reaction of degeneration.

If the lesion is in the lower motor neurone, either in the multipolar nerve cells in the anterior horn of the spinal cord, in the nerve trunk itself, or in the peripheral motor-end organs, the paralysed muscles not only undergo disuse atrophy, but rapidly waste through being cut off from their trophic centres, which reside in the spinal cord. The reaction of degeneration is also present. In this state the *nerve* supplying the muscles degenerates, and will not react to the faradic current, or to the make or break of a constant current; in these circumstances, there is therefore no response in the muscles. The muscles themselves, however, usually react to the make and break of a constant current, although the response is a *slow* contraction and not a rapid twist, and the anodal closure contraction is greater than the kathodal closure contraction; that is, the A.C.C. is > than the K.C.C.

In dealing with such cases of paralysis, where the reaction of degeneration is present, the muscles are treated with the constant current until the nerves are sufficiently recovered, so that the muscles will react to the faradic current. Treatment is then continued with the faradic current.

Electrical treatment may also be extended to "sensory" nerves. Neuralgia (a painful condition of a nerve or nerves without inflammation) may be treated by sending a *constant* current through the nerve, but the *anode* must be applied by means of rheophores (small metal discs covered with wash leather and soaked in salt solution) to the skin over the nerve. It will be remembered that, when a constant current passes through a nerve, the condition of the nerve around the anode is one of diminished excitability and diminished conductivity. This treatment therefore alleviates the pain.

CHEMISTRY OF NERVOUS TISSUE.

Fresh nervous tissue is alkaline in reaction, but turns acid after death. This is due to the formation of sarco-lactic acid, which appears first in the grey matter.

Composition.—Nervous tissue consists of the following substances:—

WATER.—70 to 80 per cent. There is more water in grey than in white matter.

SOLIDS.—*Proteins* (a large proportion)—

- Nucleo-protein, especially in the nerve cells which contain Nissl's granules.
- Globulin, coagulated at 47° C.
- Neurokeratin, most abundant in the medullary sheath.

Lipoids—

1. Phosphatides (lecithin, kephalin, sphingomyelin).
2. Galactosides (nitrogenous glucosides, which on hydrolysis yield galactose).
3. Cholesterin.

Medullated nerve appears to be richest in cholesterin and galactosides; non-medullated nerve richest in cholesterin and kephalin.

Traces of extractives and mineral salts.

STRUCTURE OF THE LOWER MOTOR NEURONE.

The lower motor neurone consists of a large *multipolar nerve cell* present in the anterior cornu of the spinal cord, and the *projection fibre* from the cell which traverses a mixed nerve in which it branches; and lastly, the *motor end-organs* present in striped muscle fibres.

The Large Multipolar Nerve Cell.—In the centre of the cell is a well-defined round nucleus, within which is the true nucleolus. In the perikaryon around the nucleus are the fine neuro-fibrillæ, which are continued into the dendrons and dendrites of the cell. These congregate at one portion of the cell, and continue on as the projection fibre or axis cylinder process of the nerve fibre which belongs to the cell. Within the protoplasm of the nerve cell, and lying alongside the neuro-fibrillæ are spindle-shaped granules (Nissl's bodies). These are also present in the dendrons, but absent from the dendrites and axis cylinder process or axon.

The Nissl bodies are readily stained with a warm weak solution (0·5 per cent.) of methylene-blue; hence they are said to consist of chromatoplasm. From a chemical point of view they are said to contain phosphorus and iron, hence they are nucleo-protein in nature. On the other hand, they become smaller, and may even begin to disappear from the cell when the cell becomes active. By some physiologists they are looked upon as one of the sources of energy of the nerve cells, hence they are said to consist of kinetoplasm. A more complete account of the structure of the neurone or morphological unit of the nervous system is described under the heading "neurone" in Chapter XXXVI.

The Nerve Fibres.—The neuro-fibrillæ of the nerve cell collect and leave the cell, together forming the axon or axis cylinder process of the nerve fibre. After the axis cylinder process leaves the grey matter it traverses the anterior root zone of the spinal cord; here it acquires a medullary sheath. A large number of such medullated nerve fibres leave the spinal cord, each acquiring a neurilemma sheath, and they then form a motor nerve root. If a transverse section of a motor nerve root is made, and the section is treated with osmic acid (1 per cent. solution), coarse medullated nerve fibres and fine medullated nerve fibres may be seen. The fine medullated nerve fibres are the visceral nerves which leave the anterior nerve root and reach the proximal sympathetic ganglion, where they form synapses with the ganglion cells (*vide* p. 563). The ganglion cells give rise to new non-medullated projection fibres which return to the neighbouring nerve. If, therefore, a transverse section of a mixed nerve (*i.e.* after the junction of the anterior and posterior nerve roots) is made, and treated with a weak solution of osmic acid, three kinds of nerve fibres may be seen, namely:—

Coarse medullated nerve fibres (lower motor and "sensory" neurones).

Fine medullated nerve fibres (vaso-dilator fibres).

Non-medullated nerve fibres (vaso-constrictor fibres).

A coarse medullated nerve fibre has the following structure: In the middle is the finely fibrillated axon or axis cylinder, and it is possible that the fibrillæ are separated from each other by an extremely fine network which also forms a very fine axis cylinder sheath. The axon conducts the nerve impulses. Surrounding the axis cylinder process is the medullary sheath. This fatty sheath consists of myelin, which consists of cholesterin and lecithin, and these substances appear to be entangled in a fine network of neurokeratin, a sclero-protein rich in sulphur. The medullary sheath is discontinuous at the nodes of Ranvier. The portion of nerve between any two nodes, which occur at regular intervals, is called the internode. At the nodes of Ranvier the axon branches. One purpose of the node no doubt is to allow tissue fluid to get to the axon for the purpose of nutrition. The outermost sheath of a nerve fibre is the primitive sheath or neurilemma, and has well-defined oval nuclei. It is slightly thickened opposite the nodes of Ranvier. The medullary sheath is probably developed from the axon, and is therefore of epiblastic origin, whereas the primitive sheath is derived from mesoblastic cells.

The Motor End-Organ.—As a medullated nerve fibre approaches the striped muscle fibres it branches. As each individual branch arrives at a striped muscle fibre the neurilemmal sheath becomes continuous with the sarcolemmal sheath of the muscle fibre. The medullary sheath stops abruptly. The fibrillated axon gives rise to extremely fine branches, some of which have little thickenings upon them. These ramify in some undifferentiated granular protoplasm within the sarcolemma of the muscle fibre, forming a motor end-organ. The fine branchings of the nerve fibres and the motor-end organs are most readily demonstrated by staining with $AuCl_3$ (0·75 per cent. solution).[1]

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[1] This is most readily done by Löwit's method. Small pieces of fresh striped muscle from a small snake are placed for one minute in a mixture

DEGENERATION OF THE LOWER MOTOR NEURONE.

When a motor nerve is cut across, at first, but for a short time only, there is a wave of increased excitability, which starts at the region of the injury and travels towards the periphery (Ritter-Valli law). This is immediately followed by a condition of diminished excitability, which also commences at the region of injury and travels towards the periphery. This condition is accompanied by Wallerian degeneration, the histological changes of which are as follows.

The axis cylinders between the section and the periphery begin to lose their fibrillations, and gradually the fibrillæ are replaced by fine granules. The medullated sheath undergoes fragmentation, becomes broken into irregular myelin droplets, and the neuro-keratin becomes less obvious. The nuclei of the neurilemmal cells multiply, invade the broken medullary sheath, and act as leucocytes in helping to remove the products of nerve degeneration to the neighbouring lymphatics.

The motor end-organs also become changed. The branched fibrillated axons which are present become granular, and the undifferentiated protoplasm appears to become more fluid and the motor end-organ to eventually shrink.

The muscle fibres supplied by the nerve *rapidly* atrophy. This change in the muscle fibres is due not only to disuse through paralysis, but also to atrophic changes which occur in the muscles themselves, for there is no doubt that the nerve cells in the anterior cornua of the spinal cord exercise some nutritional or trophic influence over the muscle fibres through the motor nerves, and when these trophic influences are cut off atrophy sets in.

If nerve regeneration does not take place, the upper portion of the lower motor neurone also undergoes degeneration from disuse, a condition known as disuse atrophy.

This change occurs first in the multipolar nerve cells.

of formic acid one part, water four parts; they are then transferred to a 1 per cent. solution of gold chloride for twenty minutes. The pieces of muscle are then transferred to the formic acid mixture for twenty-four hours, and into pure formic acid for a further twenty-four hours. After removal from the gold chloride solution, while the tissue is in the formic acid (mixture or pure), the preparation must be kept in the dark. The tissue is then worked in tap water for three hours, and pieces of the muscle mounted in glycerin and thinned out by pressure upon the cover glass. The nerve fibres and motor end-organs appear almost black.

The nucleus and the cell may show a preliminary swelling, but the cell soon begins to shrink, and its dendrites and dendrons break up. The nucleus shrinks and becomes eccentric. The Nissl spindles eventually become fine granules, and the neuro-fibrillæ become less obvious. These changes are called chromatolysis. From the point of view of the integrity of the nerve cell, however, the most important changes are those which occur in the nucleus and the neuro-fibrillæ.

As these microscopic changes are taking place in the nerve cells, Wallerian degeneration *slowly* progresses in the projection fibres between the nerve cells and the original cut which was made in the nerve (*vide* p. 480).

CHEMISTRY OF NERVE DEGENERATION.

Lecithin is one of the most important lipoids in nerve fibres, and when degeneration occurs the lecithin ($C_{42}H_{84}NPO_9$) breaks up into glycerin, fatty acids, phosphoric acid, and a poisonous alkaline choline which may be detected in the blood (*vide* p. 53).

In connection with the chemistry of nerve degeneration, Halliburton and Mott have performed a number of experiments upon cats. The sciatic nerves were divided, and the animals killed at intervals varying from 1 to 106 days. After the third day of section the nerves showed a progressive increase in the percentage of water and a progressive decrease of phosphorus, until degeneration was complete. The absorption of the products of nerve degeneration is complete earlier in the peripheral nervous system than in the central nervous system. In fact, the products of nerve degeneration in peripheral nerves are cleared away by the end of six weeks. This may be due to the power of absorption of the cells derived from the neurilemma which appear to aid the lymphatics. This chemical change in the lecithin is most readily shown by the Marchi reaction.[1]

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[1] In normal fresh medullated nerve fibres the triolein (unsaturated fat) present is in combination with the lipoid substances. Triolein reduces osmic acid to a lower oxide of osmium, which is black. In Marchi's method of staining, if normal fresh medullated nerve fibres are placed in Müller's fluid (bichromate of potash 2½ parts, sodium sulphate 1 part, water 100 parts), and then transferred to Marchi's reagent (Müller fluid 2 parts, osmic acid 1 per cent. 1 part) there is no blackening, but a greenish yellow coloration. The unsaturated fat obtains all the oxygen it requires from the bichromate of potash.

Degenerating nerve, however, contains a large amount of free unsaturated

In their experiments Halliburton and Mott demonstrated that the sciatic nerves were not excitable after the fourth to the sixth day of section, and that then degeneration sets in. From the eighth to the thirteenth day degeneration was well shown by the Marchi reaction. From the 25th to the 27th day the Marchi reaction was still observable, but the absorption of the degenerated fat had commenced. At the end of the forty-fourth day absorption of the degenerated fat was practically complete.

THE REGENERATION OF NERVE FIBRES.

It has been already stated that, if a nerve is divided, the peripheral portion undergoes rapid Wallerian degeneration, and that if the divided ends are not approximated the central portion undergoes a slow Wallerian degeneration, which commences in the nerve cells from which the fibres originally come. When nerve regeneration occurs the two ends of the divided nerve must be brought into some sort of connection. This may be done by direct suture end to end, or, if there is a gap between the divided ends, it must be filled by a piece of nerve or a piece of catgut. In either case the foreign body becomes absorbed, but no doubt first acts as a director for nerve degeneration. When new fibres are formed it is possible that they may arise in one of three ways, they may—

1. Grow down from the central end of the divided nerve; or,
2. Possibly be formed *in situ* from cells, presumably cells of the neurilemma, and then connect up with the central portion of the divided nerve; or,
3. Arise from the fibres of *other* divided nerves which wander into the old degenerated nerve sheath.

From the embryological point of view it is believed that all nerve fibres develop from nerve cells (neurone theory, *vide* p. 470), and it is only reasonable to suppose that, when part of a nerve fibre is severed from the nerve cell from which it developed, and nerve regeneration takes place, the new fibre grows from the portion of nerve fibre which is connected with the original nerve cell.

In a mixed nerve there are two sets of fibres,—those which

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fatty acid, this is due to the lipoids having been broken up. More oxygen is required to satisfy this unsaturated fatty acid. The osmic acid present in the Marchi's reagent becomes reduced, hence the blackening of degenerated nerve even in the presence of bichromate of potash.

have originated in the anterior cornual cells of the spinal cord—these are the motor fibres; and those which have originated or *grown down* from the posterior nerve root ganglion cells—these are the afferent fibres.

When a mixed nerve is cut Wallerian degeneration takes place in that part of the nerve which lies between the cut and the periphery.

It has been stated that, when Wallerian degeneration sets in, there are very definite changes in the neurilemmal cells. The nuclei of the cells multiply, and presumably gather some protoplasm around them. They then invade the medullary sheath which is breaking up, and help to remove some of the poisonous products of nerve degeneration. In this they exercise a phagocytic action. Having completed their work, these round cells again elongate, and unite to form long chains of cells, the function of which appears to be to support the new axis cylinder process which grows towards the periphery, and, having thus aided the growth of the axon, they then help to provide for the nourishment of the actively growing axis cylinder processes. It may be said, then, that the neurilemmal cells, which are of mesoblastic origin, exercise a lymphatic function during nerve degeneration, and a supporting and nutritive function during nerve regeneration.

It is generally accepted by most physiologists that new axis cylinders grow down from the central cut end of the nerve. Observations by Ross Harrison upon frog embryos go to support this view (*vide* p. 485).

The following facts support the view that, when nerve regeneration occurs, the new axis cylinder is of central origin, and grows away towards the periphery in the place of the degenerated axon.

1. New fibres arise from the central end of a cut nerve and grow in a peripheral direction. As regeneration occurs, the medullary strength is put down last in that part of the nerve which is most distant from the original cut and subsequent suture.

2. After regeneration has occurred, if the nerve is again divided between the original cut and the cord (Langley and Anderson), Wallerian degeneration takes place in all the new fibres. If, however, the nerve is divided between the original cut and the periphery (Halliburton and Mott), degeneration takes place on the peripheral side only of the

second cut. Degeneration occurs in the direction of growth, and it is concluded that regeneration also takes place in a similar direction.

3. Lugar has shown that, if the lower portion of the spinal cord is removed and the nerves connected with it cut, no regeneration occurs (*vide* p. 484).

It is only fair to state, however, that some uphold the view of "autogenetic regeneration," supposing that new nerve fibres develop from the neurilemmal sheath of the nerve fibres which have degenerated (*vide* p. 486).

CHAPTER XLVIII.

MUSCLE.

From a physiological standpoint muscles may be divided into two classes, voluntary and involuntary muscles. These possess a property common to living tissue, that of being irritable or excitable. In normal circumstances, voluntary muscles are excited through the motor nerves which supply them, but it can be readily proved that voluntary muscle is directly excitable. If the brain of a frog is destroyed (pithed), the spinal cord left intact, and a solution of curare then injected into the dorsal lymph sac which lies alongside the urostyle, the solution is distributed over the animal's body as the circulation continues. Curare poisons the motor end-organs in the voluntary muscles. If the sciatic nerve of the frog is then exposed, and stimulated electrically, the muscles of the leg will not contract, because the impulse does not reach the muscles, through being blocked at the motor end-organs. If, however, the electrical stimulus is applied directly to the muscles, they do contract. This experiment shows that muscles are excitable, and because of this *excitability* they respond to an adequate stimulus. They have the power of *contractility*.

THE CONTRACTION OF MUSCLE.

When a muscle contracts it undergoes changes in (1) *form*, in (2) *extensibility and elasticity*, in (3) *electrical condition*, also (4) *chemical changes* and (5) *changes in temperature*.

1. Changes in Form when a Voluntary Muscle contracts.

When a muscle contracts it becomes shorter and thicker. This is a change in shape only, for the volume of the muscle apparently remains the same. Certain microscopic changes may also be observed in striped muscle fibres when they contract.

The changes in form may be readily observed in the gastrocnemius of the frog, when the usual nerve-muscle preparation is made, and with such a nerve-muscle preparation, the contraction of the muscle may be recorded (a myogram). It will be shown that the contraction of the muscle varies within limits directly with the strength of the stimulus. It is influenced by temperature, by fatigue, and also by the load.

If the nerve of a nerve-muscle preparation is stimulated by a sub-maximal stimulus by means of an induction coil the muscle contracts, *i.e.* it performs a simple muscular contraction or twitch. The graphic record of such is called a simple muscle curve or myogram.

The simple muscle curve consists of three portions :—

1. **Latent Period.**—That is the period which elapses between the time when the stimulus is applied and when the muscle begins to contract. This period appears to occupy 0·01 of a second. During this time certain molecular changes occur in the nerve (nervous impulse) as a result of the stimulus, and certain changes no doubt occur in the muscle before it responds. Moreover, there is some delay (friction) in the levers used in the instrument. Allowing for these extraneous influences, the *true* latent period of muscle has been calculated at about 0·0025 of a second. The latent period is longer, however, in the red muscles of the rabbit.

2. **Contraction Period.**—As the muscle contracts and shortens the recording lever of the myograph is raised. This occupies about 0·04 of a second.

3. **Relaxation Period.**—After reaching the highest part of the curve the lever descends. This occupies about 0·05 of a second.

The simple curve may be modified by a number of factors. Those to be considered are as follows :—

(1) *The Strength of the Stimulus.*—A minimal stimulus applied to the nerve is that which is just strong enough to cause the muscle to contract. If the strength of the stimulus is increased the muscle contracts more strongly, consequently the muscle curve is higher. After a time a maximal stimulus is reached beyond which there is no increase in the amount of contraction. A strong stimulus causes the latent period to be shortened.

(2) *The Number of Stimuli.*—If a second stimulus is sent

into the nerve-muscle preparation after the result of the former is completely over, the muscle curve of the second is slightly higher than that of the preceding. This shows the *beneficial effect of contraction.*

If a second stimulus is sent into the nerve muscle preparation during the contraction of the muscle in response to the previous one, a second contraction is added to the other. This is known as *superposition*, or *summation of effects.*

If a second *maximal* stimulus is sent in during the latent period of the first simple muscular contraction there is no appreciable effect produced. If, however, submaximal stimuli are used, the two stimuli appear to be added together and the effect is a simple muscle curve, but higher than would have been produced by either submaximal stimulus alone. This is called the *summation of stimuli.*

If a number of stimuli are sent into a nerve-muscle preparation by means of a vibrating reed introduced into the primary circuit of the induction coil, and the rate of vibration is such that each succeeding stimulus arrives just after the latent period of the preceding one, the muscle contracts in response to each stimulus, and never completely relaxes between the stimuli. A condition of *incomplete tetanus* results.

If, on the other hand, stimuli are sent into the preparation so rapidly that each succeeding stimulus arrives within the latent period of the preceding one, a condition of *complete tetanus* results.

This effect may be obtained by using a rapidly vibrating reed, or Wagner's hammer, in the primary circuit. This variety of stimulation is *faradisation.*

(3) *The Load.*—The muscle contracts more steadily when the lever, which it has to raise, is loaded. As the load is increased the muscle curve becomes lower, until a stage is reached to which it is unable to lift the load.

Isotonic Curves.—If, when recording the contraction of a muscle, the load is placed vertically under the muscle, its pull on the muscle varies during the stages of contraction and relaxation owing to the inertia of the load. This variation in tension is overcome by hanging the weight as close as possible to the recording lever. When the lever is raised the weight remains practically stationary, and inertia is avoided. A muscle curve, recorded with the weight placed in the position in which the tension remains constant, is called an *isotonic curve.*

Isometric Curves.—If the muscle is fixed at one end, and made to pull against a spring so strong at the other end that, when the muscle contracts, it can move it to a slight extent only, an *isometric* curve is obtained. At first there is an increase of tension followed by a decrease. The slight movement, which indicates alterations of tension in the muscle is highly magnified. The curve which is obtained in this manner resembles the isotonic curve, except that its maximum is sooner reached and its return to its former position is also more rapid. It is probable that the isometric curve is a more faithful record of the variations in the intensity of the contraction process than that yielded by the isotonic method.

(4) *Fatigue.*—If several successive stimuli are sent into a nerve of a nerve-muscle preparation, each succeeding one not taking effect, however, until the influence of the preceding one has passed off, after a time the contracting muscle becomes fatigued.

At first the *beneficial effect of contraction* is observed, each curve being higher than the preceding one, and so on. The graphic record of this is known as *the staircase.* After a time the latent period becomes longer; the muscle takes longer in contracting; and the muscle curve is lower than previously; and, lastly, the period of relaxation becomes much lengthened. This is called *contracture.* It will be noted, then, that each phase of the contraction of muscle is influenced as fatigue sets in.

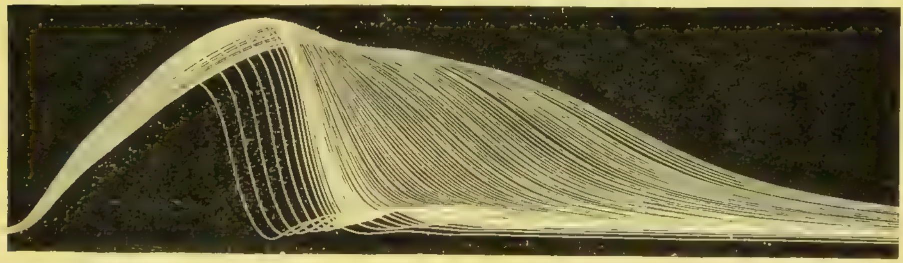

FIG. 100.—Muscle curves showing the effect of fatigue. (*After* Waller.)

(5) *The Temperature.*—If the temperature of a contracting muscle is increased by applying a warm isotonic salt solution, the effect is a shorter latent period, and a quicker and stronger contraction are the result; hence a high muscle curve. The period of relaxation may also be slightly shortened. If a higher temperature than 42° C. is applied, heart rigor occurs, which is due to coagulation of some of the muscle proteins. The effect of cold, produced by applying ice to the muscle, for example, is to increase the latent period, to increase the period of contraction (the muscle curve, however, is lower than normal), and finally, to lengthen the period of relaxation.

(6) *Drugs.*—If a weak solution of veratrine is injected into the dorsal lymph sac of a frog, after its brain has been destroyed, and the veratrine allowed to circulate for twenty minutes, a characteristic effect may be demonstrated. After contraction the muscle *begins* to relax, though a little more slowly than normally. A second small wave succeeds, and then an enormous increase of the period of relaxation. The effect, however, diminishes with repeated stimuli, but returns after rest.

The fact that fatigue, change of temperature, and drugs influence the relaxation period of the muscle curve suggests that the process of lengthening is as active as the process of shortening.

The Muscle Wave.

A muscle begins to contract in those portions which are nearest to the motor cord organs,—that is, where the nerve impulses enter the muscle. It may be assumed that, in normal circumstances, the muscle fibres constituting a muscle contract together. In a *nerveless* muscle the contraction of the fibres commences at that part of the muscle where the stimulus is sent in, and it is propagated as a wave of contraction along the muscle fibres. In a frog's muscle the wave travels at about the rate of three metres per second. The rate of the muscle wave may be increased by warmth, and delayed by cold, or by fatigue.

In a frog's muscle the rate of propagation of the wave may be measured as follows.

The muscle is previously rendered nerveless by the use of curare. The adductor muscles are removed with a small piece of bone attached at each end. The preparation is pinned out upon a myograph stand, and two light levers laid across the muscle, one at each end. These are arranged so that they write one above the other upon a revolving blackened surface. The electrodes are applied to one end of the muscle. When a single induction shock is sent into the muscle the lever nearest the electrodes rises first, and the distal lever later. The period of delay in the rise of the distal lever is measured, as well as the length of muscle between the two levers. From these data the rate of propagation of the muscle wave may be calculated.

A Voluntary Muscular Contraction.

It will be seen from the preceding paragraphs that voluntary muscles respond to a single stimulus, the result being a simple muscle contraction. Voluntary muscles also respond to a series of rapid stimuli, the result being an artificially produced tetanus. If a tracing is taken of the voluntary contraction of a muscle in the body, such as that of the opponens pollicis, it will be seen that it has small waves upon it, and is *not* the typical curve of a complete tetanus. One conclusion drawn, therefore, is that an ordinary voluntary muscular contraction, muscular tetanus, or voluntary tetanus is an incomplete tetanus. The nerve cells which send out the motor impulses are incapable of sending out a single impulse, and, in normal circumstances, are incapable of sending out impulses quickly enough to produce a complete tetanus. They are capable, however, of sending out from ten to twelve impulses per second, and these are sufficient to produce an incomplete tetanus. If, however, the nerve cells of the brain and spinal cord are under the influence of such poisons as the tetanus toxin, or strychnine, the smallest stimulus capable of producing an afferent nerve impulse results in reflex tonic, or tetanic contractions in the muscles.

2. Change in Extensibility and Elasticity when Voluntary Muscle contracts.

Extensibility.—A piece of soft putty may be easily pulled out, hence it is *extensible.* It does not return to its former shape, hence it is not *elastic.*

Elasticity.—A ball of ivory is only slightly extensible. When the stretching force is removed it returns at once to its exact original size and shape. This indicates that ivory is elastic.

A strongly elastic substance is one which offers a great resistance to an external force.

A perfectly elastic substance is one which, when stretched, returns to its original size and shape quite accurately. A ball of ivory therefore is strongly and perfectly elastic.

Living muscle within the body is very extensible,—that is, it is easily stretched. Is is, however, feebly elastic, since it offers no great resistance to any extreme force; but it is perfectly elastic, as it is returns to its original shape after being stretched. It is only when the muscle has been extended beyond the limits to which it is exposed in the body during life that this perfect elasticity is impaired.

It is found that contracted muscle is more extensible than uncontracted muscle. This increase of extensibility of muscle during contraction is protective, and tends to prevent rupture when an effort is made to lift a heavy weight.

Muscle Tone.

In normal circumstances muscles are in a state of tonicity or tonus, and, when divided, the fibres contract and the divided ends separate. Even when at rest a muscle is in a favourable condition to contract without loss of time in taking in slack. Muscle tone is under the control of the nerve cells in the spinal cord, and depends upon the integrity of the reflex arc. The sensory stimulus for reflex muscle tone is present in the muscles and their tendons, and depends upon the normal condition of the antagonistic muscles and their tendons.

Sherrington has shown that there is a "reciprocal action of antagonistic muscles" (*vide* p. 493). This means that the inhibition of the tonus of a voluntary muscle may be induced by the contraction of its antagonist. When the flexors of the knee joint contract there is an active inhibition of the tonus of the extensors which, as a result, elongate. This has been demonstrated experimentally. Electrical stimulation of the upper cut end of a motor nerve inhibits the tonus of the antagonistic muscle. In normal circumstances the reflex for the inhibition of muscle tonus may be started in the contracting muscle by way of the neuro-muscle spindles.

The tonus of antagonistic muscles (flexors and extensors) is controlled reflexly by the nerve cells of the spinal cord: flexors by their neuro-muscle spindles influencing the antagonistic extensors, and *vice versâ*.

An afferent impulse to the spinal cord, which normally produces a reflex movement, must obviously have a double action. By way of the small association neurones the nervous impulse is transmitted directly to the anterior cornual cells, which cause nervous impulses to pass directly to the contracting muscle or muscles. Probably also by collaterals belonging to the small association neurones, nervous impulses also pass to the anterior cornual cells which supply the antagonistic muscle or muscles. The influence of these impulses is inhibition of the muscle tonus in the antagonistic muscle or muscles.

If the reflex arc is interfered with, muscle tone is either diminished or completely lost.

CONDITIONS causing loss of muscle tone (hypotonus).

1. Division of posterior spinal nerve roots.

2. Disease of posterior nerve root ganglion cells, as occurs in tabes dorsalis.

3. Disease of the anterior cornual cells of the cord, as occurs in acute anterior polio-myelitis or infantile paralysis, and in chronic anterior polio-myelitis or progressive muscular atrophy.

4. Injury to motor nerves by experimental section, or from accident.

5. Paralysis of the motor end-organs, as may be produced by the administration of curare, or the presence of certain toxins (the diphtheria toxin) which cause peripheral neuritis leading to nerve degeneration.

3. Electrical Changes in Muscle.

If a voluntary muscle is removed from a frog with due care, and connected, by means of non-polarisable electrodes, with a reflecting galvanometer, it will be found that there is no movement of the spot of light which is reflected upon the scale from the mirror, which is attached to the astatic needle of the galvanometer.

If, in a similar way, also by means of non-polarisable electrodes, the voluntary muscle is connected with the platinum wires of a capillary electrometer, no movement of the mercury will be observed.

Muscle which is uninjured and at rest is *isoelectric*. If, in the investigations mentioned above, any difference of electrical potential had existed in the muscle, the spot of light reflected from the mirror attached to the galvanometer needle would have moved. The mercury contained in the capillary tube of the electrometer would have moved too, and in the direction of the negative pole. The surface of the mercury is always in a state of tension, which is readily increased or decreased by variations of electrical potential.

Current of Injury or Demarcation Current.—If a muscle is injured a variation of electrical potential at once occurs.

The injured surface becomes zincative to the uninjured part of the muscle, consequently currents arise in the injured area and travel in the muscle to the uninjured portion of the muscle. The current of injury or demarcation current may be demonstrated if a muscle preparation is arranged as in Fig. 101.

The injured end becomes like the zinc of a Daniell cell (the electro-positive element), and the current here started travels *in* the muscle to the uninjured longitudinal surface, which becomes like the copper of a Daniell cell (electro-negative element). The wire which connects the non-polarisable electrode here with the galvanometer is the anode P (galvanometrically positive), and the wire which leads back from the galvanometer is the kathode N (galvanometrically negative).

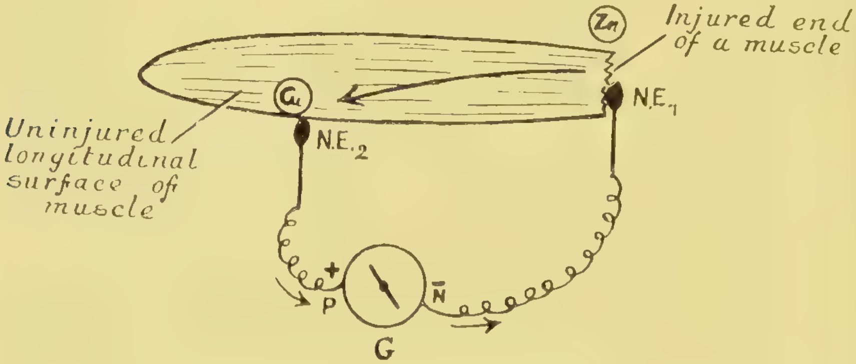

FIG. 101.—Diagram to demonstrate a "current of injury." The arrows indicate the direction of the current.

NE_1 = Non-polarisable electrode applied to the injured end of muscle.
NE_2 – Non-polarisable electrode applied to the uninjured longitudinal surface of muscle.
G = Galvanometer.

Current of Action.—When a muscle contracts there is at once an alteration from the isoelectric state to one of unequal electrical potential, and the portion of the muscle which is contracting becomes zincative to that portion which has contracted, and also zincative to that portion which is about to contract. In order to demonstrate this change, the muscle must be rendered nerveless by curare. The wave of contraction is started at one end of an uninjured muscle by sending in a single stimulus. This produces a single contraction wave. The muscle should be connected by means of non-polarisable electrodes with a galvanometer, or capillary electrometer, as in Fig. 102.

The contracting part of the muscle becomes of a higher electrical potential than the surrounding portion which has contracted, or is about to contract, and when the contraction is over the muscle returns to its previous electrical condition. This double change in the electrical condition of the muscle is called the *diphasic variation*.

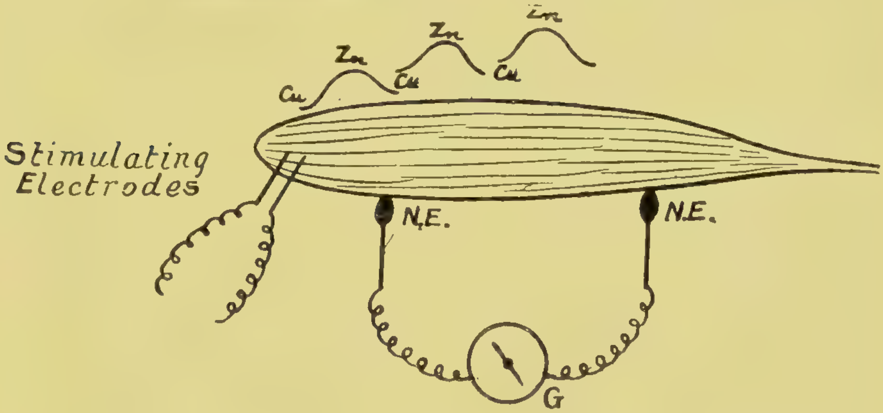

FIG. 102.—Diagram to illustrate currents of action in contracting muscle.

If, however, a wave of contraction is excited at the uninjured end of a muscle, the other end of which has been previously injured, the electrical change is a *monophasic variation*. This will be understood from the following diagram :—

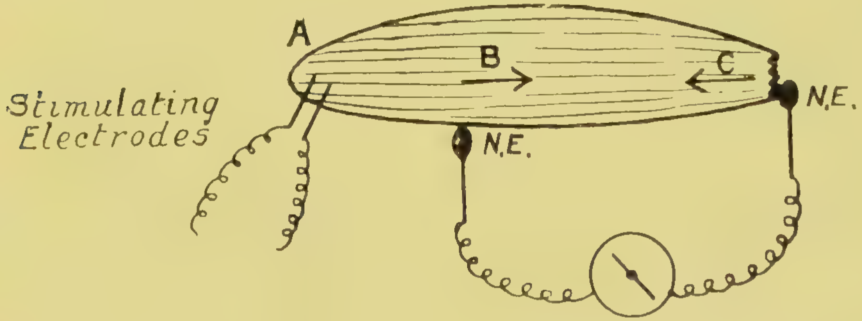

FIG. 103.—Diagram to illustrate "monophasic variation."

The contraction of the muscle commences at A, and travels towards the injured end. The electrical variation travels at the same rate as the wave of contraction, but *just precedes it* in the direction of the arrow B. As the current of action approaches the injured end of the muscle it is neutralised by the current of injury, which flows *in* the muscle from the area of injury towards the uninjured portion, as shown by the arrow C. In such a preparation, therefore, there is an electrical variation in the muscle between the two non-polarisable electrodes NE in the direction of "Zn," or electro-positive (monophasic variation), but no return to a condition of "Cu" or electro-negative.

The Physiological Rheoscope.

The electrical changes which occur in muscle, when it contracts, or is injured, are usually demonstrated, as has been pointed out, by the galvanometer, or the capillary electrometer. They may also be demonstrated by a carefully dissected muscle-nerve preparation of the frog (the rheoscopic frog). The sciatic nerve of a recently pithed and vigorous male frog is carefully dissected down to the leg, and the whole leg removed just above the knee joint; this is the rheoscopic preparation, and may be used to demonstrate electrical changes in muscle as follows:

1. *Contraction without Metals.*—The muscles of the thigh of a frog are cut transversely, and the cut nerve of the rheoscopic preparation is allowed to fall upon the injured end of the muscles, and also upon the uninjured longitudinal surface of the muscles. The *current of injury* produced in the cut thigh muscles causes impulses to travel along the nerve up the rheoscopic preparation, and the muscles of the leg contract.

2. *Secondary Contraction.*—This experiment may be carried out in two ways.

(*a*) A muscle-nerve preparation is made, and the nerve of the rheoscopic preparation is allowed to rest upon the muscle of the muscle-nerve preparation. If the muscle-nerve preparation is stimulated by a single induction shock and the muscle contracts, the rheoscopic preparation will also respond. If the muscle-nerve preparation is tetanised the rheoscopic preparation also becomes tetanised. The *currents of action* of the muscle-nerve preparation stimulate the nerve of the rheoscopic preparation.

(*b*) The heart of a vigorous male frog is carefully excised and placed upon a glass plate. The nerve of the rheoscopic preparation is placed over the beating heart from apex to base. The electrical variation, which occurs in the heart just before it contracts (current of action), causes nervous impulses to travel along the nerve of the rheoscopic preparation, which consequently responds. It should be noted that the rheoscopic preparation responds just *before* the heart beats, showing that the electrical variation occurs immediately *before* visible muscular contraction, and also that the response is a single twitch and not a tetanus. This latter fact indicates that the heart-beat is of the nature of a single muscular contraction, and is not a tetanus.

4. Chemical Changes in Muscle when it Contracts.

Resting muscle is alkaline in reaction. After repeated contractions, sarco-lactic acid is produced and the reaction is in consequence acid. The reaction of the muscles of animals hunted to death is acid.

Normal muscle, like other living tissue, contains a certain amount of loosely combined oxygen, possibly adsorbed to the fixed tissue protein. Oxidation is continuously taking place in normally toned muscles, even in their resting state, with the liberation of carbon-dioxide and water.

Carbohydrate is present in muscle, some of which (dextrose) is adsorbed to the fixed protein and some is stored as glycogen.

When muscles become active (contract) the stored glycogen is slowly converted into dextrose. The dextrose so produced, and possibly that too which is adsorbed to the tissue protein, is oxidised by the previously adsorbed oxygen and other oxygen supplied through the blood stream, to form carbon-dioxide and water. Hence active muscles give out more waste products (CO_2, H_2O, and sarco-lactic acid) than resting muscles.

A view which has been advanced is that when muscles contract, the sensory neuro-muscular spindles are so affected that afferent nervous impulses travel up to the "diabetic centre" in the medulla, which results in an increased output of dextrose from the stored glycogen in the liver. In this way the muscles provide for their own supply of carbohydrate, which is the chief source of heat and energy in the body.

5. Changes in Temperature.

It cannot be said that uncontracted muscle is in a condition of absolute rest, because it possesses *tonus*, and chemical changes are continuously occurring. As a result of oxidation processes, CO_2 and H_2O are produced, and consequently heat is evolved. When muscle contracts, work is done; oxidation becomes more vigorous and more heat is evolved.

If work is performed by a few large contractions, more chemical changes occur, more heat is produced, and fatigue sets in more rapidly than if the same amount of work was done by a larger number of smaller contractions. Halliburton puts this in a practical manner, thus: "If one ascends a tower, the *work done* is the raising of the weight of one's body to the top of the tower. If the staircase in the tower has a gentle slope, each step being low, far less fatigue is experienced than if one ascended to the same height by a smaller number of steeper steps."

The rise in temperature of frogs' muscles upon contraction may be demonstrated by a thermopile as follows:

A thermopile consists of a junction of two different metals constituting a couple (iron and German silver, or antimony and bismuth are generally used) connected by wires with a galvanometer. If the junction is heated an electrical current is produced, and the needle of the galvanometer is deflected. In the particular experiment under consideration a thermopile consisting of two sets of three couples is employed. Each set of needle-shaped couples is fixed into the two gastrocnemii of the frog. One sciatic nerve is stimulated, the muscle contracts, and the galvanometer needle is deflected, indicating a rise of temperature of that side. The other sciatic nerve is then stimulated, and a corresponding result on this side is also obtained. Helmholtz found, after tetanising frogs' muscles for two or three minutes, that the temperature rose by from 0°·14 to 0°·18 C.

Even in the resting condition the temperature of a muscle is about 0°·1 to 0°·6 warmer than the blood which supplies it, and during contraction an increase of 1°·15 has been observed in the muscles of a dog after the blood vessels had been ligatured (Pembrey).

CHEMICAL COMPOSITION OF MUSCLE.

Muscle has the following composition :—

Water	75 per cent.
Solids	25 ,,
Proteins	18 to 21 ,,
Fats	2 to 3 ,,
Carbohydrates (glycogen, dextrose) Extractives (hypoxanthine, xanthine, creatine, inosite, and sarco-lactic acid[1]	0·5 ,,
Inorganic salts, chiefly potassium phosphate	1 to 2 ,,

The Proteins of Muscle.—Muscles in the recent state contain a fluid called muscle plasma, and this may be obtained by the following methods :—

1. Frogs' muscles are cooled by ice and then subjected to strong pressure.

If a rabbit is used after it is killed, its muscles must be washed free from blood by a solution of NaCl (0·9 per cent.) injected through the aorta. The muscles should then be quickly removed and chopped into small pieces, which may then be treated as follows :—

2. By extracting the fresh muscle with 0·9 per cent. NaCl solution ; or

3. By extracting the fresh muscle with 5 per cent. solution of $MgSO_4$.

The proteins present in muscle plasma, according to the researches of Halliburton, are the following :—

Paramyosinogen. — It is a true globulin analogous to cell-globulin. It is precipitable by dialysis, and is coagulated at 47° C. *Myosinogen.*—It is an atypical globulin, and corresponds with pseudo-globulin of blood serum. It is not precipitable by dialysis. It is coagulated at 56° C. There are four times as much myosinogen present as paramyosinogen.	Most abundant.

Myoglobulin, which becomes coagulated at 63° C.

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[1] Sarco-lactic acid may be identified by means of Uffelmann's or Hopkins' reaction (*vide* p. 104).

Myoalbumin, with properties like serum albumin. It is coagulated at 73° C.

Nucleo-protein, derived from the nuclei.

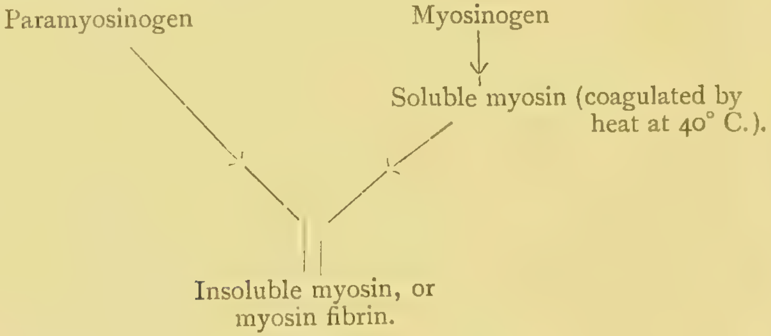
Myohæmatin, a pigment derived from hæmoglobin. On account of its affinity for oxygen, and the way it can be reduced, MacMunn considered it to be a respiratory pigment.

Collagen, a sclero-protein readily converted into gelatin.

The first four proteins may be separated from one another by fractional heat coagulation, and the first two by dialysis.

The chemical composition of unstriped muscle is much the same as that of striped muscle, except that unstriped muscle contains from six to eight times the amount of nucleo-protein found in striped muscle.

After death muscle plasma coagulates. The solid portion of the clot is insoluble myosin (myosin fibrin), and corresponds with the fibrin of a blood clot. The liquid portion is called muscle serum, and contains the myoglobulin and myoalbumin. The paramyosinogen and myosinogen are converted into insoluble myosin. It is quite possible that a myosin-enzyme helps to bring about this change, which may be represented as follows :—


Paramyosinogen
Myosinogen
Soluble myosin (coagulated by heat at 40° C.).
Insoluble myosin, or myosin fibrin.

According to v. Fürth, the myosinogen passes into a soluble condition (soluble myosin), which coagulates at 40° C. The soluble myosin, together with the paramyosinogen, then forms the insoluble myosin, or myosin fibrin.

When muscle is slowly heated it becomes contracted (heat rigor), and loses its irritability. This is due to the coagulation of the muscle proteins. If a tracing of frog's muscle is taken during the time that its temperature is being raised it will show that shortening of the muscle takes place at three stages :—

1. At 40° C.

2. At 47° C.,—the coagulation temperature of paramyosinogen.

3. At 56° C.,—the coagulation temperature of myosinogen.

In raising the temperature of the voluntary muscle of a mammal the first stage occurs at 43° C.

Brodie showed that the irritability of the muscle was lost after the first stage in the shortening, which indicates that when one of the muscle proteins has been coagulated, and the protoplasm consequently altered, muscle no longer displays one of the important phenomena of life, irritability,—in other words, the muscle has ceased to live.

Rigor Mortis.

After death, rigor mortis, post-mortem rigidity, or cadaveric rigidity sets in; that is, the muscles all over the body lose their irritability and pass into a condition of contraction. The rigidity is due to the coagulation of the muscle proteins and the subsequent formation of myosin; the muscles consequently become slightly shorter. At the same time, heat is evolved, CO_2 is given off, and the muscles become acid in reaction; this is due to the production of sarco-lactic acid and acid phosphates.

After a varying length of time the muscular rigidity passes off and the muscles become softer. This softening is probably due to the slow self-digestion, or autolysis, which occurs in the tissues, and it is brought about by the presence of intracellular enzymes, such as tissue erepsin, which have a proteoclastic action. Such tissue enzymes are said to act best in an acid medium.

Rigor mortis, as a rule, sets in first in the muscles which move the lower jaw, and then spreads to the muscles of the face and neck. The muscles of the thorax and abdomen are next affected, then those of the upper extremity, and lastly those of the lower extremity. After rigor mortis has once set in it is complete in from two to three hours. It usually lasts from twenty-four to forty-eight hours.

It rarely sets in earlier than fifteen minutes, or later than ten hours after death. In ordinary circumstances the skeletal muscles begin to stiffen about four hours after death. If sudden death occurs after violent muscular exercise, post-mortem rigidity sets in early.

Post-mortem rigidity usually ceases in the muscles in the order in which it sets in. The sooner rigor mortis comes on after death the sooner will it pass away. The converse of this is equally true.

The Non-Nitrogenous Extractives of Muscle.

Glycogen, a polysaccharide which appears to be associated with the source of muscular energy. Resting muscle contains from 0·1 to 2·5 per cent. of glycogen. The amount varies in different muscles; heart muscle is relatively rich in glycogen. During starvation glycogen disappears from the liver first, then from the muscles. The glycogen and dextrose which are present in muscle may be adsorbed to the fixed muscle protein. The glycogen in muscle is converted into dextrose by a glycolytic enzyme which is present.

Inosite ($C_6H_{12}O_6$) is an aromatic substance, its physiological importance is unknown.

Sarco-lactic acid ($CH_3.CH.OH.COOH$) is always present in dead muscle, but seems to be present in freshly excised muscle in very small quantities *only*. Fatigue due to the contraction of muscle which has been excised is accompanied by an increase of sarco-lactic acid.

Enzymes of Muscle.

In voluntary muscle the following enzymes have been found: an amylolytic enzyme which acts upon dextrose, a glycolytic enzyme which acts upon glycogen, a proteolytic enzyme which acts upon proteins, and an oxidising enzyme oxydase. These enzymes no doubt play an important part in muscle metabolism.

FATIGUE.

When a complicated voluntary muscular action is performed and repeated in a definite way over and over again, the mechanism involved appears to be somewhat as follows:—The nervous impulses originate in the pyramidal cells of the motor portion of the cerebral cortex, and travel down the nerve fibres of the brain and spinal cord in the upper motor neurone. By means of the small neurones in the grey matter the nervous impulses travel to the large multipolar nerve cells in the anterior cornua of the spinal cord. These cells transmit the nervous impulses through the lower motor neurones to the motor end organs, and by means of these structures to the muscle fibres which belong to the muscles which carry out the muscular action. The muscles which perform any complicated voluntary action must of necessity work in harmony with one another, and this fine coordination is chiefly controlled by impulses which arise in the nerve cells present in the cerebellum. Lastly, a complicated voluntary muscular action requires that the movement should be *attended to.* Attention is, in all probability, brought about by the activity of the nerve cells present in the pre-frontal lobes of the brain. It is generally accepted that the centre for the highest control (inhibition) is situated in this portion of the central nervous system.

As an example of such a complicated co-ordinated voluntary muscular action requiring active attention, an experiment with Mosso's ergograph may be described.

The instrument consists of an arm-rest, upon which the forearm is placed and strapped in position. The thumb, index, ring, and little fingers are fixed. The middle finger is placed in a movable metal stall attached to a wire which works over a pulley. To this wire various weights may be attached. Connected with the wire is a writing point, which marks upon a revolving blackened cylinder. The individual experimented upon is told to repeatedly flex the middle finger. Each time the finger is flexed the weight is raised, and the height recorded by means of the writing point. The movement is a complex co-ordinated voluntary action, which requires active attention on the part of the individual upon whom the experiment is performed. After repeated flexion of the finger the individual begins "to tire" and fatigue sets in. A typical fatigue tracing may be recorded by the writing point upon the revolving cylinder.

The *seat of fatigue* is a much debated point, and must be carefully considered. From what has been said it will be seen that the seat of fatigue *may* possibly be in any one or more of the following structures:—

1. The nerve cells which originate and control the nervous impulses.

2. The nerve fibres which conduct the impulses in the spinal cord and along the peripheral nerves.

3. The motor end organs which transmit the impulses to the muscle fibres.

4. The muscle fibres themselves.

When the fatigue of muscle artificially produced was considered (*vide* p. 601), it will be noted that the structures present were the nerve, motor end organs, and the muscle; the nerve was excited by repeated single induction shocks. Fatigue in this case is due: (i) to the consumption of those substances, especially carbohydrates, which normally exist in muscle, and which are available for the supply of muscle energy, and (ii) to the accumulation of the waste product of contraction, such as CO_2 and sarco-lactic acid. These seem to be the chief source of fatigue, for if the muscle is allowed to rest and is then washed with 0·9 per cent. NaCl solution which contains a little alkali, fatigue gradually passes off. Moreover, fatigue may be artificially produced in muscle by feeding it with a weak solution of sarco-lactic acid.

Now, if muscle is completely artificially fatigued so that it will no longer respond to a single induction shock applied to the nerve, the muscle itself *will* respond if the stimulus is applied directly to it. In other words, fatigued muscle is irritable and excitable. This suggests that the seat of fatigue is not in the muscle itself, but is either in the motor end organs, or in the nerve, or possibly in both.

An animal may be injected with a weak solution of curare until it is completely paralysed. It is then kept alive by artificial respiration. One of the nerves is exposed and then cut, and its peripheral cut end is repeatedly stimulated by induction shocks for many hours. At first there is no response in the paralysed muscles, but after the effect of the curare begins to pass off the muscles commence to respond to the stimuli. From this it is concluded that the seat of fatigue is not in the nerve fibres themselves, which have been repeatedly excited, but in the motor end organs, and that it is produced by the action of waste products such as CO_2 and sarco-lactic acid upon these structures. It is believed that the motor end organs depend upon the chemical stimulus, creatine, for their adequate working. Creatine is stored by the muscle fibres from the creatinine supplied to them in the blood stream. It is quite possible that one factor, inducing fatigue in muscle, is that the store of creatine has been used up. This may be more especially the case in the fatigue produced in a nerve-muscle preparation removed from the body, when the blood and lymph supplies are completely cut off.

In a general way it may be said that medullated nerve fibres are not fatiguable, and Waller explains this by suggesting that the katabolic changes in the axis cylinder are so slight, when it is transmitting nervous impulses, that anabolic changes are readily brought about by the medullary sheath, which appears to nourish the axis cylinder process.

By ingenious experiments upon the non-medullated nerve fibres constituting the splenic nerve, distributed in the gastro-splenic omentum to the spleen; upon the cervical sympathetic in the rabbit, and upon the splanchnic nerve of the dog, Halliburton and Brodie have shown that non-medullated nerve fibres also are, in ordinary circumstances, not fatiguable. This suggests, therefore, that Waller's explanation of the non-fatiguability of medullated nerve fibres is not quite adequate. It may be that the metabolic changes in the axis cylinders of both medullated and non-medullated nerves, when they transmit nervous impulses, are so very slight, and the products of metabolism so readily removed, that for all practical purposes it may be stated that medullated and non-medullated nerve fibres do not become fatigued. A similar statement may also be applied to the nerve fibres of the spinal cord.[1]

If, directly after fatigue has been induced by using Mosso's ergograph, as previously described, the median nerve is stimulated by induction shocks, the finger may be made to become flexed and to lift the weight again. This suggests that the seat of fatigue is in the central nervous system, and most probably is the nerve cells themselves. Moreover, the cells in the central nervous system seem to be more readily fatigued than the motor end organs, possibly because the kinetoplasm is quickly used up and acid substances produced. Eve stimulated the cervical sympathetic nerve of an animal just below the superior cervical ganglion for twelve hours, and at the end of that time there was no loss of excitability in the nerve (*i.e.* no evidence of fatigue), but he found that the nerve cells in the superior cervical ganglion stained in a *diffuse* manner with methylene-blue. This change he attributed to the presence of acid substances in the ganglion cells. A similar diffuse staining occurs in the multipolar nerve cells of the anterior cornua of the spinal cord after fatigue has been produced in them by the convulsions which have followed the administration of strychnine. M'Dougall has shown that fatigue in the brain and spinal cord has its seat, not so much in the protoplasm of the bodies of the nerve cells themselves, but rather in the arborisations of the cells. It is these arborisations which form synapses with neighbouring cells, and here nerve impulses pass with the greatest difficulty in all mental and motor processes, even when fatigue does not ensue. Mental fatigue sets in earlier when active attention (pre-frontal lobes) is brought to bear upon any subject.

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[1] It has been already explained that, when a nerve is excited, electrical variation occurs (current of action). There must therefore be some expenditure of energy, and consequently a certain amount of fatigue must arise. The loss of energy is quickly made good, for the process of repair is very rapid. Even if the induction shocks follow one another at 500 per second, there appears to be time for the nerve to recover itself. It is quite possible that this repair is brought about by the energy of the medullary sheath *and* the neurilemma, and possibly by the perifibrillar substance itself (Boruttau).

It must be remembered that the waste products which accumulate in the blood stream when muscular fatigue is induced are poisonous to the cells of the central nervous system. Mosso has demonstrated that the introduction of blood serum from a fatigued animal into the circulation of a normal animal gives rise, in the latter, to the symptoms of fatigue.

In conclusion, it may be stated that the chief seat of fatigue is in the nerve cells of the brain and spinal cord, but that it also occurs in the motor end organs; that, *in ordinary circumstances*, fatigue cannot be demonstrated as occurring either in medullated or in non-medullated nerves. The fatigue, which occurs in the muscular fibres themselves, is due to the using up of those substances present in the tissue which, when oxidised, give rise to heat and energy. As in normal circumstances these substances are readily replaced by means of the blood and the lymph, it may be concluded that, under normal conditions of nutrition, fatigue does not occur in the muscle fibres themselves.

The sensation of fatigue may be considered as a protective one, being a warning that the body needs rest. Fatigue produces a decrease in the general sensibility of the body, with the result that an individual does not attend to many discomforts which he otherwise would do; he sleeps profoundly and awakes with energy restored.

SECTION XIII.

THE SENSE ORGANS.

CHAPTER XLIX.

CUTANEOUS AND OTHER SENSATIONS.

SENSATIONS DERIVED FROM THE SKIN.

In the skin there are various end organs which, when stimulated, cause afferent nervous impulses to travel to the brain where the impulses are sensed, or where the sensation produced rises into consciousness.

The following are some of the principal end organs :—

Pacinian Corpuscles.—These are oval bodies situated in the cutis vera on the cutaneous nerves of the hands and feet; they also occur in other regions of the body, such as the mesentery and the pancreas. Each Pacinian corpuscle consists of concentric layers of fine connective tissue, each layer being lined with endothelium. Through the pedicle a single nerve fibre passes, where it loses its medullary sheath. In the centre of the corpuscle the nerve fibre consists of a naked axis cylinder, and near the distal end of the corpuscle the axis cylinder arborises. / Wagner's Corpuscle

Meissner's Corpuscles.—These are ovoid bodies consisting of connective tissue surrounded by elastic fibres, outside which there is a cellular capsule. The medullated nerve fibres wind round the corpuscle two or three times, and then lose their medullary sheath before entering it. These corpuscles are situated in the avascular papillæ of the cutis vera of the fingers and toes.

End Bulbs of Krause—These are spheroidal bodies containing ovoid cells surrounded by a thin capsule. A medullated nerve fibre enters the end bulbs, and its axis cylinder ramifies amongst the cells. These bodies are situated in the conjunctiva, glans penis, clitoris, and skin of the lips, and are also present in tendons and in the epineurium of large nerves.

Other varieties of end organs are described as present in the beak and tongue of birds, etc.

Besides the special sensory end organs described, there are fine terminal nerve plexuses consisting of branching axis cylinders. These occur in the intra-epithelial and sub-epithelial nerve plexuses of the cornea, in the deeper layers of the epidermis of the skin, and as ring-like plexuses around the hair follicles just within the outer root sheath.

By means of these different sensory end organs in the skin the following stimuli may be sensed, or, in other words, the following sensations are derived from stimuli applied to the skin,—pressure sensations, heat sensations, cold sensations, and painful sensations.

The surface of the skin appears to be divided into innumerable small "sensory areas," separated by intervals which are not responsive to those stimuli which are only just above ordinary liminal intensity. Each of these small areas or "spots" responds to a specific adequate stimulus, such as pressure, heat, cold, and pain. No doubt each area contains a special sensory end organ. The *pressure spots*, *heat spots*, *cold spots*, and *pain spots* are intermingled, but in some regions one variety predominates, in other regions another variety predominates. For the most part pain spots are most numerous (four times more numerous than pressure spots), and heat spots are least numerous. The distribution of these spots, or points, is by no means uniform.

Sensations of Pressure may normally arise from impulses originating in the whole cutaneous surface, also from the mucous membrane of the mouth, tongue, anterior nares, and the teeth. Strümpell has stated that pressure sensations may also arise in tendons, muscles, fasciæ, and the periosteum. Pressure spots are apparently most numerous about the skin of the finger-tips. Pressure sense is derived chiefly from the nerve plexuses around the hair follicles and the corpuscles of Meissner, which in hairless portions of the skin apparently replace the hairs.

Sensations of Temperature may be elicited by impulses which arise in the skin generally, the mucous membrane of the anterior nares, of the whole of the buccal cavity, of the pharynx, of the œsophagus, and about the anus.

HEAT SPOTS are particularly numerous about the skin of the cheek and forearm. The particular sensory end organs associated with heat sense have not yet been identified.

COLD SPOTS are most numerous in the skin of the glans penis. The sensory end organs are believed to be the end bulbs of Krause and the non-medullated nerve plexuses.

PAIN SPOTS seem to be distributed over the surface of the skin, but some regions are more responsive to painful stimuli than others. Pain spots have a long latent period when subjected to weak stimulation. In all probability the end organs associated with pain sensations are more superficial than those of pressure and temperature; it has been suggested, therefore, that the free nerve endings in the epidermis are the "pain end organs" (von Frey).

The responsiveness of the skin to external stimuli is investigated by æsthesiometers. Pressure sense is estimated by little weights placed upon the skin. Heat and cold sense is investigated by the use of hollow-pencil shaped rods containing hot and cold water respectively, or by using minute drops of water at different temperatures as stimuli. Pain sense is investigated by the use of fine needles.

Head's Researches.—Dr. Henry Head had the radial and external cutaneous nerves in his own arm cut near the elbow under aseptic conditions. The ends were then sutured. He noted the date and other particulars about the gradual return of function. The first sensations returned about the fiftieth day after the nerves had been divided. At this period a pin-prick was just appreciated, ice appeared cold, and water at 50 C. warm. These Head called *protopathic sensations*, and he associated them with the activity of the finely medullated nerve fibres which replaced the degenerated ones. Protopathic sensibility depends upon definite specific end organs, distributed over the skin as sensory "spots," *i.e.* heat, cold, and pain spots. When this sensibility alone is present, the spaces between these spots are insensitive to cutaneous stimuli; the heat spots react only to temperatures above 37° C.; the cold spots only to temperatures below 26° C. Heat, cold, and painful stimuli are often wrongly localised. The pressure stimuli from the skin, the intermediate temperature stimuli, the power of accurate localisation of these, the responsiveness of the spaces between the heat, cold, and pain spots, and a more definite responsiveness to painful stimuli return much later; these he termed *epicritic* sensations. By the time that these epicritic sensations have returned, it is found, by experiment upon animals, that the finely medullated nerves which are associated with protopathic sensations are admixed with a later growth of larger medullated nerve fibres, and Head believes that these are associated with epicritic sensations.

Head and Rivers have concluded from their researches that the skin is supplied by two automatically distinct systems, the protopathic and epicritic, and that these regenerate at different periods after the division and subsequent suture of an afferent nerve. Either of these systems alone may be present in certain regions.

Protopathic sensibility depends upon the existence of definite "sensory" end organs, and the areas between such organs, in the absence of epicritic innervation, are not responsive to pure cutaneous stimulation. Protopathic organs have a high threshold, the "heat spots" do not respond to temperatures below 37° C., nor the cold spots to temperatures above 26° C. The glans penis is supplied by the protopathic system only, for it is clear enough that coitus does not require a sensory mechanism of the specified grade associated with the epicritic system (M. Greenwood, Junior).

Epicritic sensibility is associated with finer and more accurate sensations. Epicritic organs have a low threshold, responding to temperatures between 26° and 38° C., and thermal adaptation is a function of the epicritic system. Epicritic organs also respond to light pressure stimuli.

SENSATIONS DERIVED FROM VOLUNTARY MUSCLE.

Between the ordinary striped muscle fibres are special bundles of fine muscular fibres surrounded by a sheath of connective tissue. Each of these organs receives a medullated nerve fibre, but the medullated sheath suddenly terminates, and the axis cylinder breaks up into secondary and tertiary branches. The latter divide into a network around the muscle fibres. These structures are the *neuro-muscular* *spindles*, and are present in most voluntary muscles, but are not found in the tongue. The neuro-muscular spindles are believed to be the sensory end organs in voluntary muscles, for the following reasons :—

1. If the anterior nerve roots are cut the nerve fibres which supply these neuro-muscular spindles do not degenerate.

2. In acute anterior polio-myelitis, a disease which involves the anterior cornual cells, the neuro-muscular spindles remain intact.

3. If the posterior nerve roots are cut the nerves supplying the neuro-muscular spindles *do* degenerate.

4. In locomotor ataxia, a disease associated with degeneration of the posterior nerve root ganglion cells, the neuro-muscular spindles degenerate.

These neuro-muscular spindles are probably all-important in "muscle sense." These sensations are appreciated when muscles actively contract, and are also appreciated when a weight is raised. The muscle sense is the chief factor in the estimation of the difference in weights (*vide* pp. 494, 495).

SENSATIONS DERIVED FROM TENDONS.

In tendons there are present the end bulbs of Krause and other "sensory" nerve terminals. Tendon sense differs from muscle sense. This may be understood from the following experiment: The forearm is flexed to a right angle with the arm, and a weight of one pound is placed upon the palm. A sensation of tension is appreciated; this is due to the sensation produced by the tension of the tendons.

Kinæsthetic sensation (sensation of movement) is due to nervous impulses arriving in the brain, which originate in the periphery in either the skin, tendons, muscles, ligaments, or synovial membranes of the various joints through which the movement takes place.

SENSATIONS DERIVED FROM BONE.

This is called vibration sense, and is usually tested by means of a tuning fork.

CLASSIFICATION OF SENSATIONS DERIVED FROM THE PERIPHERY.

I. *Sensations derived from the skin*, i.e. "*Cutaneous sensations.*" The impulses travel by cutaneous nerves	Pressure Heat Cold Pain	i. Imperfect or coarse sensations = protopathic sensations. ii. More accurate or finer sensations = epicritic sensations.
II. *Sensations derived from deep structures*, i.e. "*Deep sensations.*" The impulses travel by mixed nerves		Pressure. Muscle. Tendon. Ligaments. Synovial membranes. Bone (= vibration sense).

The impulses derived from the sensory end organs travel along the peripheral nerves (the primary or peripheral level), and the nervous impulses become rearranged in the spinal cord, where they appear to travel up definite tracks. When these afferent impulses reach the spinal cord no separation into protopathic and epicritic groups can be made out. According to Theodore Thompson, there are three ascending paths in the spinal cord, namely :—

1. For *all* forms of painful and thermic impulses.
2. For pressure impulses.
3. For impulses connected with sense of position.

SENSATIONS OF SMELL.

Sensations of smell are derived from nervous impulses which arise in the olfactory mucous membrane, which is present upon the upper part of the superior turbinated bone and the corresponding portion of the septum nasi.

Structure of the Olfactory Mucous Membrane. — The olfactory mucous membrane (Schneiderian membrane) is of a yellow colour, and consists of two parts, the superficial or epithelial layer and the deeper layer or corium.

The epithelial layer consists of three kinds of cells :—

1. OLFACTORY CELLS.—These are specialised nerve epithelial cells. Each is columnar in shape, with a central oval nucleus. The peripheral part of the cell is somewhat narrow, and perforates the cuticular lamina ; it ends in hair-like filaments. The basal part of the cell is somewhat varicose, and has non-medullated nerve fibres arborising around it.

2. Columnar or Sustentacular Cells.—These cells have a broad peripheral portion ending at the cuticular lamina; they are not ciliated, and are not connected with nerve fibres.

3. Tapering Cells.—These are columnar, with a broad basal portion towards the corium and a tapering portion towards the cuticular lamina. These cells are not ciliated, and are not connected with nerve fibres. The columnar cells and the tapering cells are supporting in function (*vide* Fig. 104).

In the thin corium there are blood vessels, non-medullated nerve fibres, and simple serous glands. The serous glands of Bowman consist of acini which are lined by cubical cells supported upon a basement membrane. The watery secretion of these glands passes out between the epithelial cells to the surface of the Schneiderian membrane.

Nerve Connections of the Olfactory Cells.—The non-medullated nerve fibres, which arborise around the varicose bases of the olfactory cells, pass back through the holes in the cribriform plate of the ethmoid bone to the under surface of the olfactory bulb. These nerves then form synapses with one of the peripheral dendrons of the mitral cells, so producing an olfactory glomerulus. The projection fibre of a mitral cell becomes medullated, and travels back in the olfactory tract to the base of the brain. It must be remembered, however, that the olfactory tract and bulb (the rhinencephalon) are in their early stage of development hollow outgrowths of the brain, and therefore, strictly speaking, remain portions of the brain. The olfactory tract in many animals remains hollow, but in man the cavity becomes obliterated by the development of neuroglia. From the olfactory bulb the olfactory tract passes backwards towards the region of the anterior perforated space at the base of the frontal lobe. Here the olfactory tract bifurcates into a lateral and a mesial root. Some fibres in the lateral root pass to the olfactory cortex at the tip of the hippocampal region (the uncinate gyrus), other fibres pass back to the optic thalamus. The fibres in the mesial root pass across the middle line of the brain in the anterior white commissure to reach the uncinate gyrus of the opposite side. The anterior commissure also contains fibres which pass from the hippocampal region of one side of the brain to that of the opposite side. It will be noted that the olfactory path does not traverse the internal capsule of the corpus striatum, therefore the sense of smell is unaffected in lesions of that region.

With regard to the sense of smell, animals are divided into three classes :—

Anosmatic animals with no sense of smell (the porpoise).

Microsmatic animals with a feeble sense of smell (man).

Macrosmatic animals with a good sense of smell (the dog).

The adequate stimulus for the olfactory cells is an odorous substance in a *gaseous* state. In order that such stimuli may take effect, they must be sniffed up into the superior meatus of the nose. If a nasal catarrh occurs, the sense of smell is to a very considerable extent lost, because the swollen condition of the mucous membrane prevents the odorous gases reaching the cilia of the olfactory cells. Anosmia (loss of the sense of smell) may occur from disease of the mucous membrane of the nose, or from nervous causes (especially functional diseases). Temporary anosmia may be induced by the local application of cocaine or morphia. Hyperosmia (increased sensibility to odorous stimuli) and parosmia (perverted sense of smell) also occur in functional disease

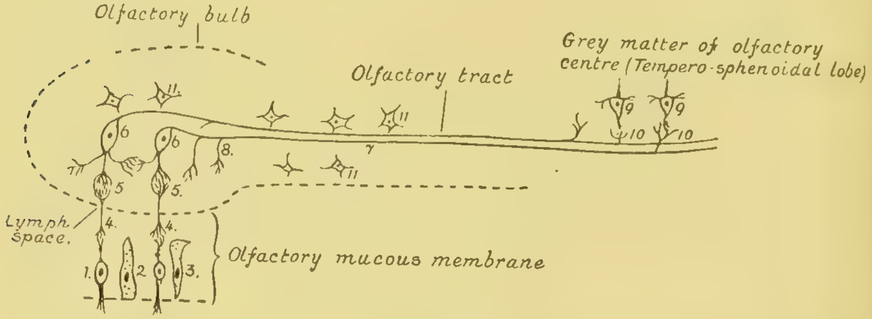

Olfactory bulb
Olfactory tract
Grey matter of olfactory centre (Tempero-sphenoidal lobe)
11
11
11
11
6
6
7
7
8.
9
9
10
10
5
5.
4.
4.
Lymph. space.
1.
2
3.
Olfactory mucous membrane

FIG. 104.—Diagram of the nerve connections along the olfactory tract.

1=Olfactory cell.
2=Sustentacular cell.
3=Tapering cell.
4=Non-medullated nerve fibres.
5=Olfactory glomeruli.
6=Mitral cells.
7=Medullated nerve fibres.
8=Collaterals to olfactory bulb.
9=Triangular cells of cortex of temporo-sphenoidal lobe.
10=Collaterals to the cells of temporo-sphenoidal lobe.
11=Neuroglial cells.

The layers of the olfactory bulb from without inwards are :—

1=Non-medullated nerve fibres from the olfactory mucous membrane.
2=Olfactory glomeruli, these are synapses.
3=Mitral cells.
4=Medullated nerve fibres.
5=Neuroglial cells.

(hysteria). Temporary hyperosmia may be induced by the administration of strychnine.

Solutions of camphor (1 in 1000 to 1 in 1,000,000) are generally used to test the sense of smell. In some cases the delicacy of the sense of smell is remarkable. It has been calculated that the gas given off from $\frac{3}{100000000}$ of a grain of musk is an adequate stimulus for the olfactory cells, and may therefore be sensed.

SENSATIONS DERIVED FROM THE TONGUE.

Structure of the Tongue.—The tongue contains two sets of striped muscle fibres: (1) the *extrinsic muscles*, by which it is attached to surrounding structures, such as the lower jaw, hyoid bone, styloid process, and palate; these muscles produce the coarser movements of the tongue; (2) the *intrinsic muscles*, which are called the linguales muscles. These run in various directions, and by them the finer movements of the tongue are performed. Amongst the muscle fibres are small serous glands, the ducts of which open on to the dorsal aspect of the tongue. Those which open into the moats of the circumvallate papillæ are called the glands of Ebner. On each side of the middle line, underneath the tip of the tongue, is a gland (Blandin and Nuhn) the shape of an almond. The pit-like openings of the ducts of the glands are on the under surface of the tongue near the tip. At the back of the tongue, behind the foramen cæcum, and embedded in the substance of the tongue, is a mass of lymphoid tissue called the lingual tonsil.

The mucous membrane of the dorsal and ventral surfaces of the tongue is covered with a stratified epithelium. On the dorsal aspect the corium of the mucous membrane forms numerous projections which contain connective tissue, blood vessels, and nerves. These projections are covered with the stratified epithelium, and form the papillæ of the tongue. There are four varieties of papillæ on the dorsum of the tongue:—

1. CONICAL PAPILLÆ.—These cone-shaped papillæ occur fairly evenly distributed over the dorsum of the tongue, but particularly over its middle portion.

2. FILIFORM PAPILLÆ.—These are fine projections upon

some of the conical papillæ; some conical papillæ have more than one such projection.

The conical and filiform papillæ are probably associated with the sense of pressure derived from the tongue.

3. FUNGIFORM PAPILLÆ.—These occur at the sides and tip of the tongue, a few are present on the dorsum. They are probably associated with the sensation of taste.

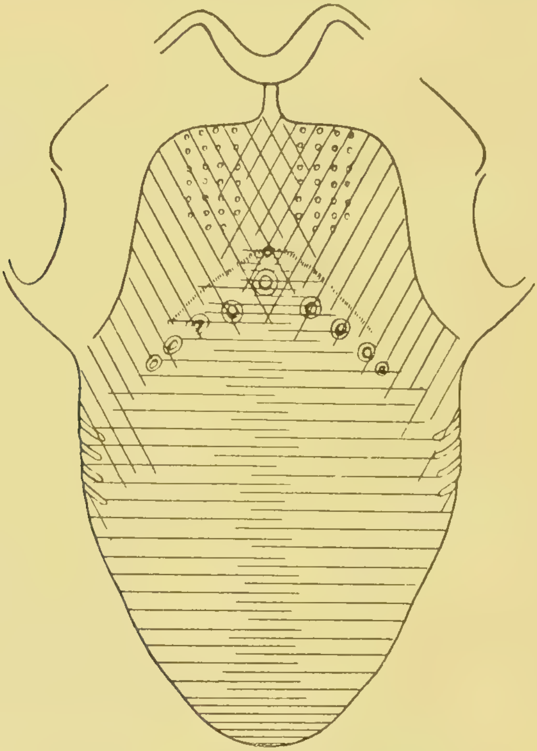


FIG. 105.—Diagram of the dorsal aspect of the tongue. (*From* Schäfer *after* Haycraft.)

The horizontal lines indicate the distribution of the lingual nerve, including the chorda tympani.

The oblique lines indicate the distribution of the glossopharyngeal nerve.

The small circles indicate the distribution of the superior laryngeal nerve.

The larger circles indicate the position of the circumvallate papillæ.

4. CIRCUMVALLATE PAPILLÆ.—These are present on the posterior part of the dorsal aspect of the tongue. There are eight or ten of these papillæ arranged thus Λ, the apex of which points to the foramen cæcum. Around each papillæ is a moat which receives the ducts of the simple serous glands of Ebner. In the stratified epithelium, covering the sides of the circumvallate papillæ, are the *taste buds*.

Structure of the Taste Buds.—Taste buds are present in the stratified epithelium of the posterior third of the tongue, of the wall of the pharynx, soft palate, and posterior surface of the epiglottis. Each taste bud consists of two kinds of columnar epithelial cells, the gustatory and the sustentacular cells; scattered between these are a few lymphocytes.

Each gustatory cell is a highly specialised nerve-epithelial cell. Around the central oval nucleus the protoplasm is granular. The free end of the cell tapers, and has a single cilium. The base of the cell also tapers, and around it are the fine arborisations of nerve fibres. The cilia of the gustatory cells project through the opening of the taste bud, which is called the gustatory pore.

The sustentacular cells are columnar and finely granular. They are not ciliated, and are not connected with nerve fibres. Their function appears to be to support the highly specialised gustatory cells.

Nervous Supply of the Tongue.—The hypoglossal is the motor nerve of the tongue, supplying both the intrinsic and extrinsic muscles. The afferent nerve from the posterior third of the tongue is the glossopharyngeal, and from the anterior two-thirds the lingual. The lingual contains chorda tympani fibres (*vide* Fig. 105). If the chorda tympani nerve is cut, and the central cut end stimulated electrically, chemically, or mechanically, sensations of taste are produced. It is generally accepted that the glossopharyngeal nerve is the special nerve of taste for the posterior third of the tongue, and that the chorda tympani fibres (through the lingual nerve) are the fibres which convey the nervous impulses associated with taste from the anterior two-thirds of the tongue.

The sensations derived from the tongue are those of *pressure*, *heat*, *cold*, *pain*, and the special sense of *taste*.

TASTE.—In order that substances may be tasted they must be in solution; this suggests that the adequate stimulus is a chemical one. There are four taste sensations, sweet, acid, bitter, salt. Sweet solutions are more readily appreciated at the tip of the tongue, acid solutions at the sides and upper surface, bitter solutions at the back, and salt solutions generally over the surface. If a solution of cocaine is painted upon the dorsal surface of the tongue, bitter sensations are blunted, and finally abolished. A sodium salt of gymnecic acid (gymnema sylvestre) finally abolishes sweet and bitter sensations, though it has no effect upon the impulses arising from salt and acid stimuli. In all probability there are four different sets of end organs, each of which has its specific adequate stimulus.

The nervous impulses associated with taste appear to travel back to the hind brain in the fibres of the glossopharyngeal nerve. Those impulses, which arise in the anterior two-thirds of the tongue, travel in the chorda tympani fibres of the lingual nerve through the facial nerve, and, by communicating fibres, through the tympani plexus of nerves, thence through the tympanic branch (Jacobson's nerve) of the glossopharyngeal nerve to the glossopharyngeal nerve itself. It is believed by many neurologists that the nervous impulses associated with taste travel back to the brain not only by way of the glossopharyngeal nerve, but also by the "sensory" fibres contained in the fifth cranial nerve (trigeminal), and partly through the pars intermedia, or the "sensory" root of the facial nerve.

The centre for taste appears to be situated in the anterior inferior temporo-sphenoidal lobe of the brain on its external and mesial aspects.

The peripheral organs associated with the senses of smell and taste are placed in immediate relation to the first part of the alimentary canal, in order that, so far as possible, unwholesome food may not be allowed to enter the digestive tract. In other words, the organs of smell and taste are essentially protective.

SENSATIONS DERIVED FROM THE VISCERA.

Painful sensations may arise from most organs, if they are injured or inflamed. A painful sensation is one of the local symptoms of inflammation, and indicates the necessity for physiological rest to arise, and when rest is allowed the early stage of repair usually commences. As a rule, painful sensations do not arise from the organs of the thorax, abdomen, and pelvis, but directly the parietal layer of a serous membrane is injured or inflamed, painful sensations occur. If the parietal layer of the pleura, of the pericardium, or of the peritoneum is injured or inflamed, painful sensations arise, and the muscles over the painful area, so far as possible, become reflexly contracted. No doubt this is a protective measure, and helps to keep the inflamed area at rest.

Referred Pain.—Head has shown that, if certain stimuli are applied directly to the viscera, painful sensations do arise. The sensation of pain, however, is not referred to the viscus in which it really arises, but is referred to some cutaneous surface. The area of cutaneous reference is constant, and, apart from the actual pain, appears to be hyperæsthetic. It may be that the posterior nerve root ganglion, which receives fibres from the viscus, and from the corresponding cutaneous area, forms the connecting link.

Sensations of thirst arise from the back of the pharynx, and are a protective signal to warn the individual that fluid is required by the body. Artificial drying of the back of the pharynx will cause sensations of thirst to arise.

Sensations of heat and cold arise from the œsophagus, for the sensations of warmth and cold, which arise when hot or cold liquids and solids are swallowed, are almost entirely referable to this organ, and not to the stomach.

Sensations of hunger are the outcome of nervous impulses from the stomach, possibly from the excitation of the nerve endings in its mucous membrane. Possibly the adequate stimulus is a "condition of emptiness" of the stomach, for to a considerable extent the sensation of hunger may be overcome by swallowing water.

Sensations of nausea which are distinctly affective, and are therefore true feelings (*vide* p. 708), are due to abnormal nervous impulses from the mucous membrane of the stomach itself.

SENSE OF POSITION.

The sense of position may be divided into two types: (1) the sense of position of one's own body and limbs with regard to oneself; (2) the sense of position of one's body to the external world.

1. **The Sense of Position of One's Own Body in Space,** whether upright or horizontal, etc., is brought about by an association of ideas and previous experience, due to the sensations derived from muscles, tendons, ligaments, synovial membranes, and skin, together with pressure sensations derived from the membranous labyrinth. "The sense of position is *perhaps* referable to the end organ of the utricle. The sensory

epithelium of the utricle differs from that of the semicircular canals in having a mass of small solid particles (otoliths) applied to the hairs. It is clear that with varying degrees of rotation of the head the extent to which the hair cells are pulled on by the otoliths will be altered; it is also evident that, so long as the new position is maintained, the stimulation will endure. This mechanism therefore provides for a long-continued excitation, and would be a basis for the origin of general sensations of position" (Greenwood.) At the same time, visual sensations may be called to our aid.

If a limb is moved passively its position is sensed by the impulses from skin, muscles, tendons, ligaments, and synovial membranes. In the disease, tabes dorsalis, these impulses may not arrive at the brain, hence a tabetic may be unable to locate the position of a limb moved passively if he has been previously blindfolded. Directly, however, visual impulses are allowed to operate the position of the limb in space is accurately localised. When in doubt we use our eyes, for, to a very considerable extent, "seeing is believing."

2. **Sense of the Position of One's Body in Relation to the External World**, *i.e.* the sense of orientation.

The knowledge of the position of one's body in relationship to one's surroundings is due to the association of ideas produced by sensations derived from the impulses from the sensory end organs in the skin (pressure sense), muscles, tendons, ligaments, and synovial membranes; also from the muscles of the eyeballs; also from impulses which arise from the end organs in the membranous labyrinth, and, most important of all, from the visual sensations derived from the retinæ. The portion of the brain which appears to be most concerned with the sense of orientation is the occipital convolutions. If a previously normal individual is completely deprived of his vision through disease in the eyes, he is still capable of finding his way about (sense of orientation); whereas, if the occipital regions of the brain were completely diseased, he would be deprived of that sense. Animals, especially dogs, also utilise the sense of smell to a marked degree in aiding them in locating their position in relationship to external objects. The ideas associated with previous experience (memory) no doubt play an important part in the sense of orientation.

Forel states that "the faculty of orientation outside the body itself is the result of the experience of known senses, combined or not, especially of sight and smell, according to the case and the species. In aerial orientation it is vision which most predominates."

The case of the carrier pigeon constitutes the best example of aerial orientation. In terrestrial orientation the sense of smell often plays a prominent part, but in animals, and especially in man, the sense of smell gives way to the sense of sight.

THE EYE.

CHAPTER L.

THE STRUCTURE AND FUNCTIONS OF THE EYE.

THE EYELIDS.

THE upper eyelid consists of a layer of thin skin underneath which is loose areolar tissue without fat. In the skin there are fine hairs and small sweat and sebaceous glands. Beneath the skin there are the striped muscular fibres forming the orbicularis palpebrarum. Deep to the muscle is the tarsal plate of dense fibrous tissue, to which the striped muscle fibres of the middle portion of the levator palpebræ superioris are attached.

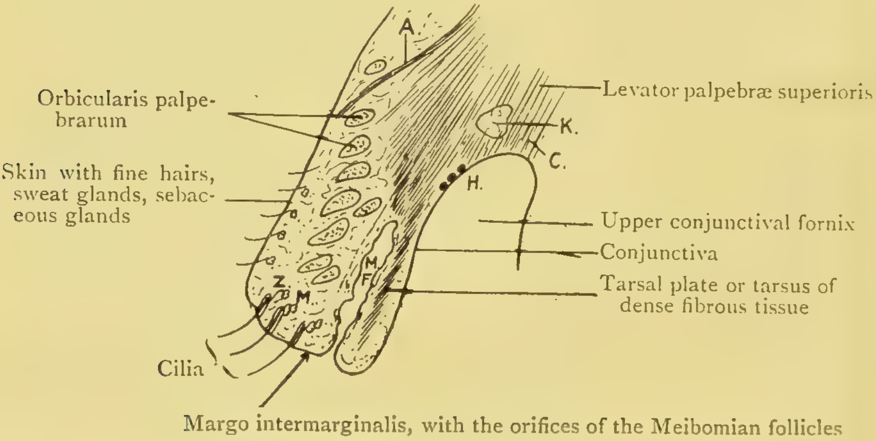

A.
Levator palpebræ superioris
Orbicularis palpebrarum
K.
C.
Skin with fine hairs, sweat glands, sebaceous glands
H.
Upper conjunctival fornix
Conjunctiva
M.
F.
Z.
M.
Tarsal plate or tarsus of dense fibrous tissue
Cilia
Margo intermarginalis, with the orifices of the Meibomian follicles

FIG. 106.—Sagittal section of the upper eyelid. (*After* H. J. Parsons.)

M.F. = Meibomian follicle.
Z. = Gland of Zeiss, sebaceous follicle of cilium.
M. = Gland of Moll, a large sweat gland, the duct of which opens into the gland of Zeiss or into the hair follicle.
H. = Glands of Henle.
K. = Gland of Krause.

Some of the anterior fibres of the levator palpebræ superioris run forward to the skin A (*vide* Fig. 106), while some of the posterior fibres are attached to the conjunctiva C.

Scattered in the connective tissue of the upper lid are plain muscle fibres, forming the muscle of Müller, which is supplied by the sympathetic nerve. This muscle is inserted into the upper border of the tarsal plate. In the substance of the lid are the Meibomian follicles, which secrete an oily material. On the under surface is a layer of conjunctiva, the palpebral conjunctiva, which is reflected on to the anterior surface of the eyeball.

The structure of the lower eyelid resembles that of the upper, except that the tarsal plate is less defined, and the levator palpebræ is obviously absent.

The function of the lids is to protect the eyeball, and to lubricate the ocular conjunctiva.

THE LACHRYMAL APPARATUS.

Each lachrymal gland consists of three parts,—the superior or orbital gland, situated in the lachrymal fossa ; the inferior or palpebral gland, consisting of one or two lobules lying under the conjunctiva ; and the accessory glands of Krause. There are numerous small acini lying in the conjunctival fornix. In structure these are all racemose glands, very like the serous salivary glands. The orbital gland has ten to thirteen ducts, which pour their secretion into the upper and outer part of the conjunctival sac. In normal circumstances there are just enough tears secreted to keep the surface of the eye moist. If there is a slight increase in secretion of tears they are conducted across the conjunctival sac towards the inner canthus of the eye, when they escape down the puncta lachrymalia, through the lachrymal canaliculi into the lachrymal sac, and through the nasal duct into the inferior meatus of the nose. If the surface of the conjunctiva is irritated by a foreign body there is reflexly produced an increased secretion of tears, the purpose of which is to wash away the foreign body from the eye, and, in these circumstances, more tears are secreted than can escape through the puncta lachrymalia, hence they flow on to the cheek. The conjunctiva and canaliculi are lined by a stratified epithelium, the lachrymal sac and nasal duct by a columnar epithelium.

The lachrymal secretion is a slightly alkaline fluid containing sodium chloride. It has slight antiseptic properties.

THE EYEBALL.

The outer coat of the eyeball consists of the sclerotic coat or sclera, which is continuous behind with the fibrous sheath of the optic nerve, and in front with the cornea. The fibrous sheath of the optic nerve is continuous through the optic foramen with the dura mater. Internal to the fibrous coat of the eye is the vascular coat, consisting of the choroid, the ciliary body, and the iris; this constitutes the uveal tract. Internal to the vascular coat is the nervous portion of the eye, the retina. This is continuous behind with the fibres of the optic nerve, and in front it ends irregularly at the ora serrata. Internal to the retina is the fine hyaloid membrane, which completely surrounds the vitreous humour contained in the vitreous humour chamber. The lens, surrounded by its capsule, lies immediately behind the iris, the central aperture of which is the pupil. Between the anterior portion of the capsule of the lens and the posterior surface of the cornea is the aqueous humour chamber. This is incompletely divided into two portions by the iris: the portion in front of the iris being known as the anterior chamber of the eye, and the portion between the iris and the anterior portion of the capsule of the lens as the posterior chamber of the eye. These two chambers communicate through the pupil. Covering the cornea and the anterior portion of the sclera is the ocular conjunctiva; that portion of the conjunctiva, which is reflected over the inner aspects of the upper and lower eyelids, is known as the palpebral conjunctiva. The conjunctiva is intimately connected with the anterior surface of the cornea, but where it is reflected on to the sclera and the eyelids there is some sub-conjunctival loose connective tissue. The greater portion of the globe is surrounded by a form of synovial membrane or socket known as the capsule of Tenon; this capsule is reflected along the tendons of insertion of the muscles which move the eyeball. Anteriorly, Tenon's capsule is covered by a portion of the conjunctiva.

Tenon's capsule contains fine fibrous tissue and an inner lining of endothelial cells. In its walls are plain muscle fibres which are innervated by the sympathetic. It will be seen, then, that the eyeball is surrounded by a serous membrane which enables it to move smoothly. If the muscle of Tenon's capsule definitely contracts, the eyeball is pushed slightly forwards, a condition called exophthalmos; this occurs when the cervical sympathetic nerve is irritated. On the other hand, when the plain muscle in Tenon's capsule is paralysed, as occurs when the sympathetic nerve in the neck is cut, the eyeball recedes slightly, a condition called enophthalmos.

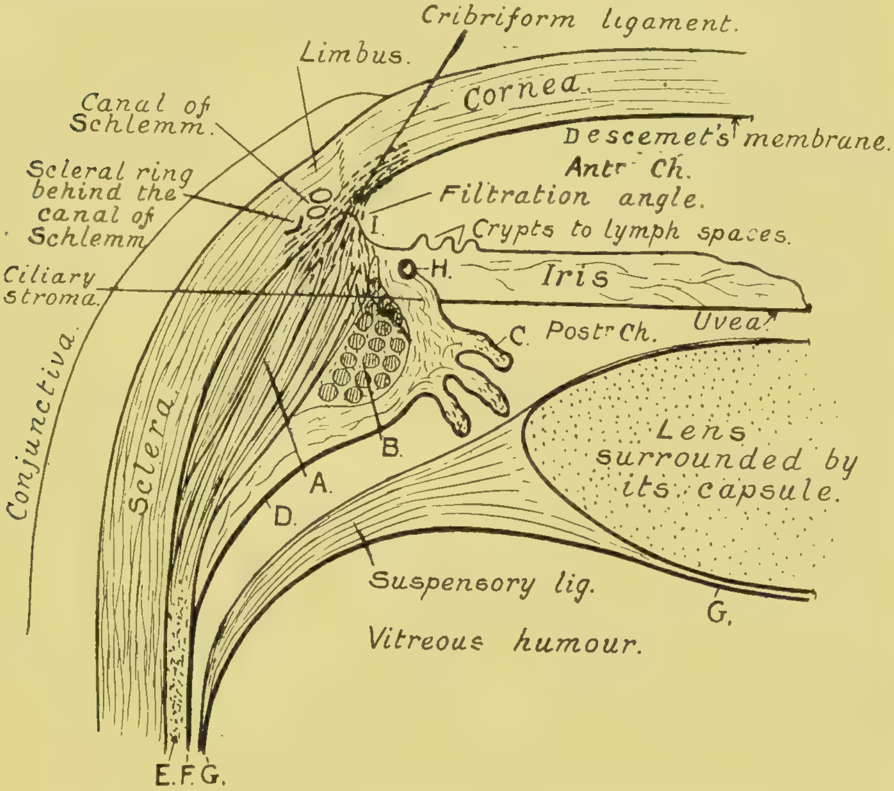


FIG. 107.—Section of the anterior part of the eyeball.

A=Antero-posterior or meridional fibres of Brücke } Ciliary muscle.
B=Circular fibres of Müller.
C=Pars plicata with ciliary processes, these contain vascular tufts.
D=Pars plana of ciliary body covered with pigment cells.
E=Vascular choroid, between it and the sclera is the suprachoroidal space.
F=Retinal pigment continued forward over the pars plana.
G=Hyaloid membrane.
H=Vein at the base of the iris.
I=Spaces of Fontana in the cribriform ligament, situated at the filtration angle.

The Conjunctiva.—The conjunctiva consists of a stratified epithelium of about ten or twelve layers of cells. Where it is reflected over the cornea it is intimately attached to it, forming the anterior layer of the cornea. The conjunctival sac is kept moistened by the tears (lachrymæ).

The Cornea.—This is the transparent part of the front of the eye, and is continuous at its margins with the sclerotic coat, and where they join (sclero-corneal junction) the sclera overlaps the cornea all round its periphery, forming the limbus. The cornea in the adult is about 1 mm. thick, and is made up of the following parts: anteriorly is the stratified epithelium, the deeper cells of which are columnar. Ramifying between these cells is the intra-epithelial plexus of very fine nerves, which end in small thickenings between the cells. The stratified epithelium of the cornea represents the reflection of the conjunctiva. The epithelium is supported by the anterior homogeneous layer of Bowman. Beneath the epithelium is the corneal tissue proper, consisting of transparent fibrous tissue, the fibres of which cross one another at right angles. Between the fibres are minute lymph canals (the canals of Recklinghausen), which communicate with one another and with the corneal tissue-fluid spaces. In these tissue-fluid spaces are irregular connective-tissue cells, sometimes known as corneal corpuscles. The function of the lymph or tissue-fluid is to nourish the substance of the cornea. This fluid is derived from the aqueous humour, and enters the cornea through the spaces in the cribriform ligament at the filtration angle. Beneath the anterior homogeneous layer of Bowman is the fine sub-epithelial nerve plexus, and in the substance proper of the cornea is the primary nerve plexus of non-medullated nerve fibres derived from the ciliary nerves. These nerve plexuses are extremely fine, and in places have a beaded appearance. At the back of the cornea is the transparent elastic lamina of Descemet; this stops short of the filtration angle.

On the posterior surface of Descemet's membrane is a single layer of flattened epithelial cells. These line the anterior part of the aqueous humour chamber, and are reflected around the angle between the cornea and the anterior portion of the ciliary body on to the iris itself. This angle of reflection is the corneo-iridic or filtration angle. According to Thomson Henderson, the inner corneal lamellæ, in the neighbourhood of the corneo-iridic angle, continue on as the *cribriform ligament*, which ends as the ligament of origin of the ciliary muscle. The cribriform ligament consists of both circular and longitudinal fibres, which enter in equal proportions into the composition of its whole structure. The circular fibres of the cribriform ligament are continuous with the circularly arranged connective-tissue bundles surrounding the venous canal of Schlemm. These circular fibres help to keep the ciliary muscle in position.

The longitudinal fibres of the cribriform ligament are not derived from a splitting up of Descemet's membrane, as is usually stated, but are a direct continuation backwards of the innermost lamellæ of the cornea.

The longitudinal fibres may be divided into two sets,—the outer or scleral set, and the larger or ciliary set.

The outer or scleral set of fibres forms a small part only of the cribriform ligament. These fibres run backwards, but internal to the canal of Schlemm. At the posterior extremity of this canal they become continuous with the fibres of the sclera.

The inner or ciliary fibres spread out in a fan-shaped manner, and form the ligament from which the fibres of the ciliary muscle arise.

The Sclerotic Coat or Sclera.—This is the toughest coat of the eyeball, and mainly consists of white fibrous tissue, but it also contains a small amount of yellow elastic tissue. (This may be demonstrated by staining with an alcoholic acid solution of orcein.) On its outer aspect it has an endothelial lining derived from the capsule of Tenon, and on its inner aspect a layer of brown pigment cells called the lamina fusca. This coat is pierced at the back (porus opticus) by the optic nerve, which enters the eyeball towards the nasal side. Here the thin coat, containing connective-tissue fibres and elastic tissue, is known as the *lamina cribrosa*. Inserted into the sclerotic, just behind the cornea, are the tendons of the muscles which move the eyeball; namely, the superior rectus, the superior oblique, the interior rectus, the inferior rectus, the inferior oblique, and the external rectus. In some animals the sclera contains cartilage.

Internal to the sclerotic coat are the choroid and the ciliary body, and these are connected with the sclerotic by loose connective tissue. Pervading this loose connective tissue is tissue-fluid, and the space between the choroid and the sclerotic is known as the perichoroidal lymph space, or the suprachoroidal space.

The Uveal Tract.—The uveal tract consists of the vascular coats of the eye; these include the choroid, the ciliary body, and the iris, and these structures are more or less continuous with one another.

The Choroid.—The choroid coat is the vascular coat in the back portion of the eye. It lies between the sclerotic coat and the retina; it is mainly vascular, and its function is to nourish the pigment cells, the rods, the rod fibres, the cones, and the cone fibres of the retina. The blood vessels to the choroid are derived from the short posterior ciliary arteries which pierce the sclerotic coat at the back of the eyeball. The choroid consists of the following layers: On the outside is the lamina supra-choroidea, which contains elastic fibres and scattered pigment cells; internal to this is a layer of large blood vessels; internal to these is a layer of medium-sized blood vessels; and more internal still is a layer of extremely fine blood vessels called the chorio-capillaris layer. These three layers of blood vessels are held together by a stroma which contains branched pigment cells. Internal to the chorio-capillaris layer is a thin elastic membrane known as the *lamina vitrea*, or the membrane of Bruch. The choroid is supplied by sensory nerves from the ophthalmic division of the trigeminal. In front the choroid becomes continuous with the ciliary body.

The Ciliary Body.—This lies just behind the corneo-scleral junction, and is continuous behind with the choroid and in front with the iris. The inner aspect of its posterior portion is smooth, and is known as the *pars plana* of the ciliary body. The inner aspect of the anterior portion is thrown into folds, and is known as the *pars plicata*; on this there are in all about seventy ciliary processes. External to these two portions, and adjacent to the sclerotic, is the muscular portion of the ciliary body.

The Ciliary Muscle.—The ciliary muscle is unstriped, and consists of two definite portions. The outer portion of antero-posterior fibres, which constitute Brücke's muscle; and the inner portion of circular fibres, which constitute Müller's muscle.

The fasciculi of Brücke's muscle consist of two distinct parts,—the outer and larger longitudinal muscle bundles, and the inner and smaller longitudinal fasciculi. These fibres arise at the corneo-scleral junction, from the internal or muscular division of the cribriform ligament, which is derived from the innermost lamellæ of the cornea. The fibres pass backwards, and are inserted partly into the choroid coat and partly into the suspensory ligament of the lens. It will be noted that the scleral ring is not the point of origin of the ciliary muscle, but is simply the fixed part which steadies the cribriform ligament during the contraction of the muscle.

The circular fibres of the ciliary muscle (Müller's muscle) form a true ciliary sphincter connected by interstitial tissue with the most internal fibres of the cribriform ligament, the fibres of which constitute a check ligament to these circularly arranged muscular fibres. These circular fibres support the base of the iris. It will be noted, then, that the innermost fibres of the cribriform ligament act as a ligament of origin for the longitudinal fibres of the ciliary muscle, and as a check ligament to the circular fibres.

The fibres which constitute the ciliary muscle are supplied by the inferior division of the third cranial nerve.

The *pars plana* of the ciliary body is covered on its free surface by cubical epithelial cells which contains pigment granules; these cells are supported by a basement membrane, and are a continuation forward of the pigment cells of the retina, and are continued forwards as the pigment cells present upon the ciliary processes.

The *pars plicata* of the ciliary body has on its inner aspect the ciliary processes, of which there are in all about seventy. Each process arises from a base which is continuous with the stroma of the root of the iris. Between the ciliary processes are the interciliary grooves, which are continued anteriorly on to the back of the iris as radial furrows. The interciliary grooves are lined by cubical cells which contain pigment, and these cells are directly continuous with the uveal pigment cells present on the posterior surface of the iris. Over the ciliary processes are two sets of cells, a deep set of pigment cells and a superficial set of columnar non-pigmented cells. These latter, in all probability, secrete the aqueous humour. Embedded in the connective tissue in the ciliary processes themselves are numbers of capillary tufts not unlike the kidney glomeruli. The long posterior ciliary arteries supply the ciliary body. The sensory nerves of the ciliary body are derived from the ophthalmic division of the fifth cranial nerve. Anteriorly the stroma of the ciliary body is in relationship with the aqueous humour chamber, and it helps to form the corneo-iridic angle. Internally and anteriorly the ciliary stroma is continuous with the iris stroma, —and the basement membrane of the ciliary body, which supports the pigment cells, is continuous anteriorly with the posterior limiting membrane of the iris which supports the uveal pigment cells.

The Functions of the Ciliary Body.—The ciliary body has two main functions:—

1. *It contains the Ciliary Muscle, which is one of the Muscles of Accommodation.*—When the antero-posterior fibres contract they draw the choroid and the hyaloid membrane slightly forwards; this relaxes the suspensory ligament of the lens. The result is that the anterior surface of the lens moves slightly forwards. When the circular muscle fibres contract they squeeze the circumference of the lens, and so cause its anterior surface to move forward. The posterior surface does not bulge backwards, as it is supported by the semisolid vitreous.

2. *The Ciliary Processes produce the Aqueous Humour which is the Tissue-Fluid of the Eyeball.*—There are two views with regard to the origin of the aqueous humour.

(1) That it is a true secretion formed as the result of the physiological activity of the columnar cells which cover the free portions of the ciliary processes.

(2) That it is a transudation from the capillary tufts of vessels which lie in the ciliary processes.

If it is true, as Thomson Henderson suggests, that the intraocular pressure stands at intravenous pressure, filtration is not possible. Since the same hydrostatic pressure exists on both sides of the "filtering" membrane, then aqueous humour must come wholly from the cells over the ciliary processes.

The aqueous humour is secreted somewhat slowly, for if a wound occurs in the cornea and all the aqueous humour escapes, and the corneal wound then becomes sealed over, it is at least an hour before the aqueous humour is again secreted in sufficient quantity to completely re-form the aqueous humour chamber. In these circumstances some of the new aqueous humour produced may be derived from the capillaries in the ciliary processes, for the pressure in the aqueous chamber falls with the escape of aqueous humour.

THE FUNCTION OF THE TISSUE-FLUID IN THE EYEBALL.—The function of the aqueous humour is chiefly nutritive. It nourishes the avascular parts of the eye, such as the cornea, the crystalline lens and its capsule, the suspensory ligament of the lens, the vitreous humour, and the hyaloid membrane. The aqueous diffuses through the meshwork of the cribriform ligament at its origin, and so gains access to the tissue-fluid spaces present in the cornea.

Measurement of Intraocular Tension.—This may be done in animals by inserting a fine cannula into the aqueous humour chamber in front of the iris, and connecting it with a small narrow-bored mercurial manometer. In this way it may be shown that the intraocular pressure is capable of supporting a column of 30 mm. Hg.—that is, the normal intraocular pressure is 30 mm. Hg. above the atmospheric pressure. The pressure in the vitreous humour chamber may also be estimated in a similar way. It is found experimentally that in the "closed" eyeball the pressures in the aqueous and vitreous chambers are the same. The intraocular pressure or tension in man may be readily estimated by the fingers. The examiner stands in front of his patient, whom he directs to look downwards (not to shut his eyes), the little, ring, and middle fingers of each hand are supported on the patient's face and forehead, and the tension of the eyeball estimated by gently alternately pressing the index-fingers upon the upper eyelid as it covers the sclera.

The Circulation of the Tissue-Fluid of the Eye.—The aqueous humour, which is very watery, containing only 0·045 per cent. of protein, is derived from the ciliary processes. It has been calculated that about forty-nine fiftieths of it pass to the posterior part of the aqueous chamber; then, between the posterior surface of the iris and the anterior part of the capsule of the lens, forwards through the pupil into the anterior part of the aqueous chamber. In this passage forward it is aided by the contraction of the iris. The aqueous humour then passes outwards to the corneo-iridic or filtration angle, through the spaces of Fontana, which are in the network of the cribriform ligament (T. Henderson), thence to the venous sinuses constituting the canal of Schlemm, and thence into the anterior uveal veins. Some of the aqueous humour which has passed through the meshwork of the cribriform ligament at the filtration angle gets through the fibres of origin of the ciliary muscle, thence into the perichoroidal lymph space, and is taken up by the posterior uveal veins. Some of the aqueous humour passes in through the crypts of Fuchs, which are present near the base of the iris, and eventually is taken up by the veins present in this situation, and finally gets into the anterior uveal veins which drain the iris and ciliary body. The anterior uveal veins cross the supra-choroidal space. A smaller portion, it is said about one-fiftieth of the aqueous humour, passes from the ciliary processes through the meshes in the suspensory ligament of the lens into the vitreous humour chamber, and so to nourish the vitreous humour, thence by the canal of Cloquet, which is a perivascular lymph canal around the remains of the hyaloid artery, which originally ran from the central artery of the retina to the back surface of the lens. From the canal of Cloquet the fluid travels to the perivascular spaces around the central vessels of the retina, thence to the optic nerve and the vaginal space or lymph space, which lies between the optic nerve and its fibrous sheath of dura mater, thence the fluid passes back into the sub-arachnoid space. The blood in the canal of Schlemm, and that in the plexus of capillaries around the ciliary muscle, returns by way of the anterior uveal veins, which pierce the sclerotic coat near the pericorneal circumference. The blood from the iris veins runs back through the ciliary plexus of capillaries, present in the ciliary processes, and the blood from this region returns by the posterior uveal veins, or venæ vorticosæ, of which there are four.

The Iris.—The iris is the coloured diaphragm which lies between the anterior and posterior portions of the aqueous humour chamber. The hole in the centre is the pupil. The base of the iris is continuous with the anterior part of the ciliary body, and through the cells on its anterior surface the iris is connected anteriorly with the posterior surface of the cornea.

Structure of the Iris.—On the anterior surface is a basement membrane on which is a single layer of flattened cubical cells, which are continuous round the corneo-iridic angle with the flattened cells on the back surface of the cornea. The posterior surface of the iris is covered by a double layer of cubical cells which contain pigment granules. These cells are continuous with the pigment cells of the ciliary processes, which, in their turn, are continuous with the pigment cells over the pars plana of the ciliary body, and these again are continuous with the pigment cells of the retina. The pigment cells on the back of the iris are called the uvea, and are supported on a basement membrane. Between the two basement membranes in the iris there is a delicate loose connective tissue, scattered in the meshwork of which are pigment cells, which give the dark colour to the iris. In this connective tissue there is a network of capillaries, and near the base is the circulus iridis major, which receives the iris veins. The circulus iridis major vein also receives tributaries from the ciliary veins. The iris is thinnest at its base, where it is attached to the ciliary body, and in this neighbourhood there are small crypts through which the lymph spaces between the stroma cells communicate with the anterior part of the aqueous chamber. These crypts of Fuchs lead the aqueous humour into the iris veins. In the connective tissue of the iris there are two sets of plain muscular fibres:

1. *The Sphincter Pupillæ, most developed near the Pupillary Margin.*—This is supplied by the inferior division of the third nerve.

2. *The Dilator Pupillæ.*—This muscle consists of isolated radial fasciculi arranged around and in front of the radial furrows, which are present directly anterior to the posterior limiting membrane of the iris. The fasciculi of the dilator pupillæ arise from the innermost strands of the cribriform ligament. From this origin the isolated fasciculi of the dilator pupillæ course radially inwards, to terminate by a direct insertion into the connective-tissue stroma of the sphincter pupillæ (Thomson Henderson). The dilator pupillæ is innervated through the cervical sympathetic.

Branches derived from the nasal branch of the ophthalmic division of the fifth nerve constitute the "sensory" nerves of the iris.

It has been demonstrated by Thomson Henderson that the circulus iridis major is a venous canal, and that the iris crypts communicate with it. The iris crypts and veins constitute auxiliary areas for the escape of aqueous humour. Dilatation of the pupil closes the mouths of the iris crypts, and in this way tends to interfere with the escape of aqueous humour, while contraction of the pupil helps to open the iris crypts, and so facilitates the escape of the aqueous humour from the anterior part of the aqueous humour chamber into the veins at the root of the iris.

FUNCTION OF THE IRIS.—By means of the iris is regulated the amount of light rays which enter the eyeball, and consequently inpinge upon the retina. At the same time, by its contraction, the iris regulates the size of the pupil, the consequence of which is that central rays and those near the optic axis only are allowed to traverse the lens. In this way *spherical aberration* and *chromatic aberration* are reduced to a minimum. The result of this is that, in normal circumstances, images of external objects formed on the retina are well defined and have no coloured edge. The following diagram will make spherical aberration more readily understood.

The parallel rays *a* entering the lens near its optic axis are refracted and brought to a focus at *a′*; those marked *b*, which enter the lens farther away from the optic axis, are brought to a focus at *b′*;—this obviously causes a blurred image due to spherical aberration. The iris cuts off these peripheral rays, such as *b*, and prevents this blurring. White light is composed of the colours of the spectrum, and the rays due to the various colours are refracted differently, the violet rays are most and the red least bent. When white light rays traverse a lens there is a tendency for them to be split up into their component parts. The image so produced will have a coloured edge; this phenomenon is chromatic aberration. This again, to a very considerable extent, is prevented by the contraction of the iris cutting off the peripheral light rays.

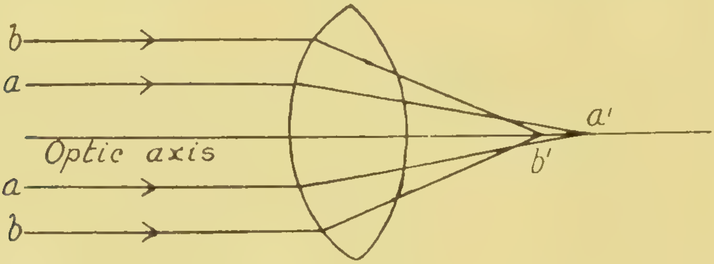


FIG. 108.

THE INNERVATION OF THE IRIS.—*The Myotic Tract.*—In the anterior part of the third nerve nucleus, which is placed alongside the aqueduct of Sylvius and underneath the anterior corpus quadrigeminum, is a group of nerve cells which give rise to fibres which innervate the sphincter pupillæ. These fibres travel through the trunk of the third nerve, traversing its inferior division, thence through the nerve which supplies the inferior oblique muscle of the eye, thence to the ciliary or lenticular ganglion, where they form a cell station, arborising around the nerve cells there. The fibres, which arise in these nerve cells, leave as the short ciliary nerves, and pass forward piercing the sclerotic coat of the eye, and then travel forwards between the sclerotic and the choroid to the sphincter pupillæ. It is generally believed that the ciliary ganglion is a peripheral motor nucleus controlling the sphincter pupillæ.

2. *The Mydriatic Tract.*—The nerve centre, which gives rise to the fibres which control the dilator pupillæ, is most probably present in the mid-brain near the third nerve nucleus. From this centre fibres pass down through the pons and medulla, and through the lateral columns of the spinal cord. These fibres then arborise around cells in the grey matter of the spinal cord, situated at the level of the first, second, and third dorsal segments. These cell stations give rise to new fibres, which leave the cord by the anterior nerve roots of the first, second, and third dorsal nerves, and also probably by the last two cervical nerves. The fibres then pass directly into the first dorsal or stellate ganglion, then by the anterior limb of the annulus of Vieussens into the inferior cervical ganglion. The fibres travel up the cervical sympathetic through the middle into the superior cervical ganglion, where the fibres for the dilator pupillæ arborise around nerve cells. The superior cervical ganglion is therefore a cell station upon the mydriatic tract. The cells here give rise to new fibres which pass along the sympathetic nerve plexus on the internal carotid artery, and in this way reach the skull. The fibres then leave the carotid artery and run over the anterior part of the Gasserian ganglion, and pass into the ophthalmic division of the fifth nerve, traversing the nasal division. They leave that nerve as the long ciliary nerves which pierce the sclerotic on each side of the optic nerve. The fibres run forward between the sclerotic and choroid, entering the ciliary body, and so get to the dilator pupillæ. It will be seen then that the cell station for the sphincter pupillæ is in the ciliary ganglion, and the cell station for the fibres, which supply the dilator pupillæ, is in the superior cervical ganglion.

Circumstances in which the Pupils contract (Miosis).—

1. When rays of light traverse the eyeball, that is, when light falls upon the retina, the pupil of the same side contracts. This

is the direct light reflex, and the course of the impulse is as follows: The rays of light traverse the eyeball, and are brought to a focus on the retina; here they travel through the layers of the retina from within outwards, until they fall on the receptive part of the retina which is the specialised sensory nerve-epithelium; this includes the rods and the rod fibres, the cones and the cone fibres. The function of these is to convert the light stimulus into an afferent nerve impulse, which travels back through the retina from without inwards, passing through the first neurone in the internal nuclear layer of the retina, thence to the second neurone or the ganglion cell, and from the ganglion cells through the nerve fibres back along the optic nerve to the anterior corpus quadrigeminum. In the anterior corpus quadrigeminum the third neurone starts, from which the nerve impulse passes to that part of the third nerve nucleus which innervates the sphincter pupillæ muscle. The impulse passes from these cells along the third nerve, through its lower division to the ciliary ganglion, through this cell station and by way of the short ciliary nerves to the sphincter pupillæ; hence the contraction of the pupil takes place.

2. If rays of light traverse the media of one eye, not only the pupil of that eye contracts, but also the pupil of the opposite eye. This is the consensual light reflex; it is brought about by the cells in the part of the third nerve nucleus which form the centre for the sphincter pupillæ, and which constitute a single nucleus. In all probability this single collection of cells innervates both sphincters pupillæ.

3. When the eyes are focussed at a near object; this focussing is the accommodative synkinesis.

4. When the eyeballs converge.

5. During sleep (in this state, as a rule, most sphincters remain contracted).

6. On direct stimulation of the optic nerve, the anterior corpus quadrigeminum, the anterior part of the third nerve nucleus, or the third nerve itself.

7. After section or paralysis of the cervical sympathetic nerve.

8. Under the influence of drugs, some of which act upon the centre for the contraction of the pupil, and others act peripherally,—*e.g.* opium and morphia produce bilateral myosis; this is due to central action. Pilocarpine, eserine, and muscarin

act locally by stimulating the nerve endings in the sphincter pupillæ muscle. Under the influence of these drugs the pupil still further slightly contracts when exposed to light, and slightly dilates in the dark.

✓ **Circumstances in which the Pupils dilate (Mydriasis).**—

1. In the dark (dark adapted eye), or if the retinæ are non-responsive to light.
2. When accommodation is relaxed.
3. During dyspnœa, and in the later stages of asphyxia.
4. During deep emotion.
5. When stimuli from the skin result in painful sensations, especially those arising from the skin of the neck.
6. During stimulation of the upper cut end of the cervical sympathetic, and as a result of general sympathetic irritation.
7. Paralysis of the third nerve, when the dilator pupillæ contracts unopposed.
8. Under the influence of drugs, some of which act centrally and others peripherally,—*e.g.*, curare causes dilatation of the pupil through stimulation of the centre for the dilator pupillæ muscle. Atropine acts locally by paralysing the nerve terminals in the sphincter pupillæ muscle; it also paralyses the nerve terminals in the ciliary muscle, and, under its influence, the pupil will not re-act to light directly or consensually, nor will it react to accommodation. Cocaine causes dilatation of the pupil by stimulating the sympathetic nerve terminals in the dilator pupillæ muscle. During chloroform anæsthesia the pupil in the early stage becomes slightly dilated, but during chloroform narcosis the pupil should remain contracted; if, however, the narcosis is too deep the pupils dilate.

✓ **Argyll-Robertson Pupil.**—In certain diseases, such as locomotor ataxia and general paresis of the insane, the pupil does not react reflexly to light, but reacts to accommodation. This condition is known as the Argyll-Robertson phenomenon, and Marina has shown that the condition is associated with degeneration of the cells in the ciliary ganglion.

The Vitreous Humour.—The vitreous humour is a clear jelly-like material which occupies the vitreous humour chamber, and is completely surrounded by the hyaloid membrane. It contains a few small branching cells, the branches of which form a network by joining with branches of other cells. In this meshwork there is much intercellular material. The vitreous humour is pervaded with tissue-fluid derived from the ciliary processes, and in this fluid there are wandering amœboid cells. In the earlier stages of the development of the eye, the central artery of the retina traversed the vitreous humour as the hyaloid artery, and terminated at the back of the crystalline lens. In birds and some mammals a vascular organ projects from the optic disc into the vitreous. Structurally this is homologous with the ciliary process, and is known as the pecten. Normally the hyaloid artery atrophies, but its perivascular lymph space around persists and is known as the canal of Cloquet. The vitreous humour is surrounded by a fine structureless membrane known as the hyaloid membrane, which is attached to the ciliary body in the neighbourhood of the free margin of the retina.

The Zonule of Zinn.—In the neighbourhood of the ora serrata a fibrillated membrane, called the zonule of Zinn, or the suspensory ligament of the lens, is attached. It is continued into the cellular capsule of the lens. Aqueous humour circulates in the meshwork of the fibres of the suspensory ligament. This space in the meshwork, which contains the aqueous, is called the canal of Petit. The ciliary muscle is partly inserted into the hyaloid membrane and into the suspensory ligament of the lens.

The Crystalline Lens.—Structurally this consists of elongated nucleated clear cells known as lens fibres, most of which grow from the epithelium on the posterior surface. The lens is developed as an invagination of the epiblast; it is at first hollow, but later becomes solid from proliferation of epiblastic cells lining its cavity. The nucleus of the lens consists of its oldest cells, and the peripheral part or cortex contains the youngest cells.

At quite an early stage the productive basal cells are limited to a row of cubical cells covering the anterior surface of the lens. The lens is surrounded by a fine cellular membrane, the lens capsule, which is thicker on its anterior than on its posterior aspect. The lens is held in place by the suspensory ligament. In the fœtus the lens is nearly spherical, but it gradually becomes flattened antero-posteriorly, and in the adult it is biconvex, being flatter (when accommodation is relaxed) upon its anterior surface.

Chemically the lens consists of a globulin called crystalline. If put into water the lens swells and splits, the split on the anterior surface is Y-shaped with the base of the Y vertical.

In normal circumstances, the anterior surface of the lens supports the back surface of the iris and steadies the iris in its action. If the lens is dislocated backwards the iris becomes tremulous, a condition called irido-donesis.

Elementary Physiological Optics.

The cornea is a curved plate with parallel sides, and this acts very much like a second lens in the eye; the object of this arrangement (cornea and lens) is to diminish the focal distance of the eye.

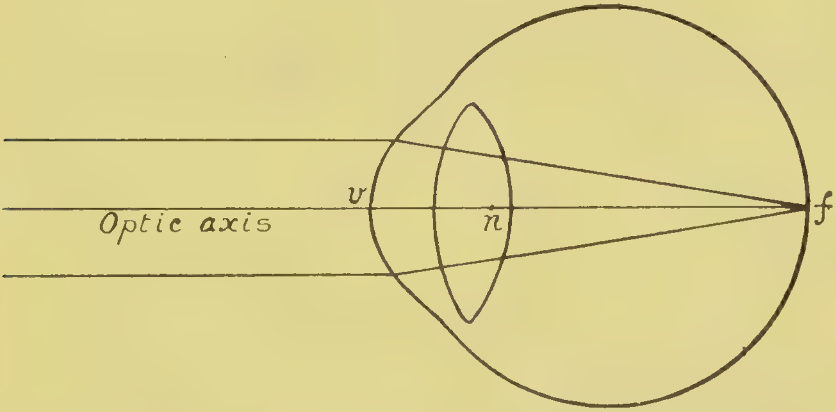


FIG. 109.—Diagram representing the normal (human) eye, in which the principal focus is on the retina, 23 mm. behind the cornea.

v=Vertex of the curved cornea.
n=Optical centre of lens.
f=Fovea centralis (principal focus).

The centres of curvature of the cornea and of the two surfaces of the lens are on the same straight line or optic axis.

When a ray of light meets the cornea it is deflected towards the normal, and passes through the layers of the cornea in the new direction, and continues in the same direction through the aqueous humour; for the refractive index of the aqueous is the same as that of the cornea. When the ray of light meets the anterior surface of the lens, which has a greater refractive index than the aqueous humour, it becomes again more deflected towards the normal, and therefore towards the optic axis. If parallel rays fall upon the cornea they are brought to a focus 23 mm. behind it. In this way parallel rays which enter the pupil from a distant object are brought to a focus at the principal focus of the eye, which is 23 mm. behind the cornea; and this distance is exactly that of the retina from the cornea in the normal human eye. The optic axis when produced backwards meets the fovea centralis of the retina. It will be seen, then, that, in the normal or emmetropic eye, when in a condition of rest, parallel rays are brought to a focus upon the retina.

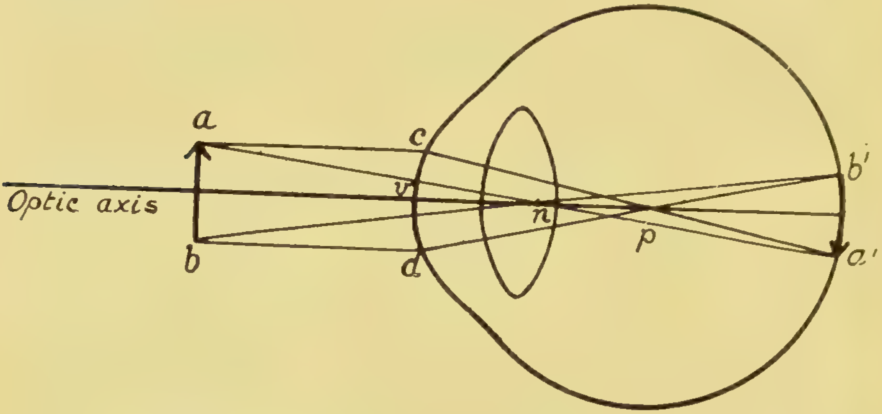


FIG. 110.—Diagram to represent the "reduced eye," *i.e.* the eye reduced to a simple optical system.

v=The vertex of the curve of the cornea.

n=Position of the "nodal point" or optical centre of the eye. This point is situated on the optic axis of the eye, about 0·47 mm. in front of the posterior surface of the lens.

p=Posterior principal focus, situated about 22·64 mm. behind the anterior surface of the vertex of the cornea.

The optic axis is a line drawn through v and n, and, when prolonged through the eye, cuts p, the posterior principal focus.

A ray of light from *a* traversing the nodal point *n* is not refracted, but passes straight on to a^1 on the retina.

A ray of light *ac*, which is parallel to the optic axis, entering the cornea at *c*, is refracted whilst traversing the cornea and lens. It traverses the point *p*, which is the posterior principal focus, and reaches the retina at a^1.

In a similar manner rays of light from the point *b* traverse *n* and *p* respectively, and are brought to a focus upon the retina at b^1.

The object *ab* produces an inverted image b^1a^1 upon the retina.

The image, however, is re-inverted psychologically in the brain.

The angle *anb* is called the visual angle, and is the angle at the nodal point which is subtended by the object.

The *horopter* is the term applied to that surface in the outer world which contains all those points, rays of light from which fall upon identical points of the two retinæ.

If the visual lines are parallel, the horopter will be a plane at an infinite distance (*vide* Fig. 111).

If the visual lines converge, as is the case when a near object is being looked at, the horopter is a circle which passes through the nodal points of the two eyes, and also through that fixed point in the outer world at which the eyes are focussed, the image of which falls upon the two maculæ. The images of other points in this circle horopter fall upon identical points of the retinæ (*vide* Fig. 112).

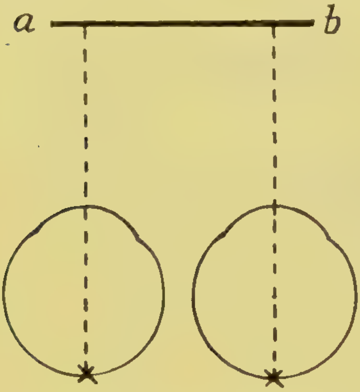


FIG. 111.

a, *b*=The horopter when the eyes are parallel.

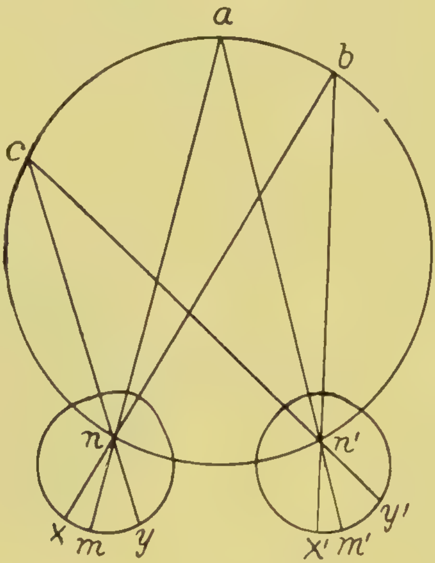


FIG. 112.

a=A point in the outer world (point of regard), at which the eyes are focussed. Divergent rays of light traverse the nodal points *n*, n^1, and are focussed on the maculæ *m*, m^1, which are corresponding points in the retinæ.

Rays of light from *b* traverse the nodal points *n*, n^1, and are focussed upon *x*, x^1, which are corresponding points in the retinæ.

Rays of light from *c* traverse the nodal points *n*, n^1, and are focussed upon *y*, y^1, which are also corresponding points in the retinæ.

In other words, objects lying on the horopteric circle are seen as one.

Accommodation.—It has been shown that, in an emmetropic eye (normal eye) at rest, parallel rays are focussed upon the retina. For all practical purposes parallel rays may be considered as coming from a distance of 20 feet (6 metres) away and beyond. As an object is brought nearer to the eye than 20 feet it emits divergent rays, and in order that a clear image may be obtained on the retina the divergent rays are converged by an increase in the convexity of the crystalline lens. When an object is brought to 10 inches distance from the eyes (ordinary reading distance) full "restful accommodation" is brought to bear. *Accommodation* may therefore be defined as the changes which take place in the eye when one looks at a near object, the usual distance of which is about 10 inches from the eye; if the eyes are normal, accommodation may take place up to within 5½ inches of the eye (in the adult), and this is called the near point of accommodation (punctum proximum).

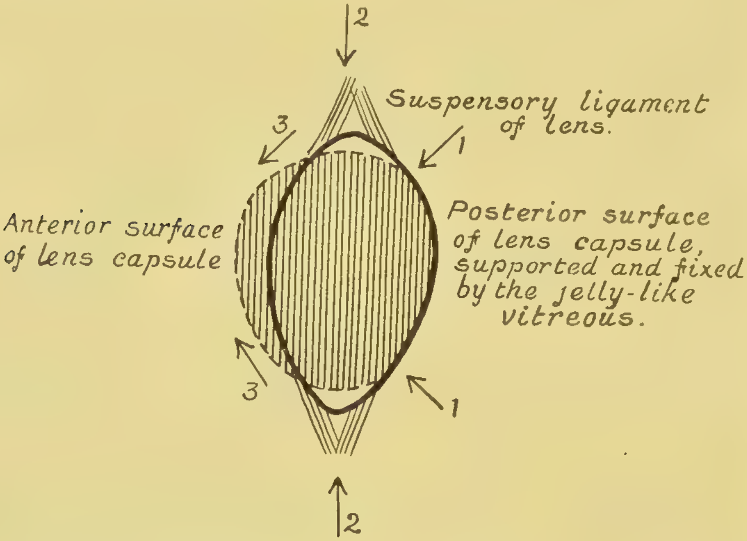

2
Suspensory ligament of lens.
3
1
Anterior surface of lens capsule
Posterior surface of lens capsule, supported and fixed by the jelly-like vitreous.
3
1
2

FIG. 113.—The crystalline lens.

Arrows 1 indicate the direction of the pressure of the vitreous.
Arrows 2 indicate the direction of the pressure of the circular fibres of the ciliary muscle.
Arrows 3 indicate the direction of movement forward of the anterior part of the lens within its capsule, which is somewhat relaxed during accommodation.

THE CHANGES WHICH TAKE PLACE IN THE EYE ON ACCOMMODATION.—1. *The Pupil contracts.*—This is due to the action of the sphincter pupillæ, which is innervated by the third nerve. This movement of the iris is associated with the accompanying act of convergence, rather than with accommodation *per se.* It is probably of the nature of an associated movement or synkinesis (J. H. Parsons).

2. *The Lens becomes more Convex.*—This change takes place on its anterior surface,—that is, the anterior surface bulges slightly forward. These changes in the plastic lens are brought about by the action of the ciliary muscle. The

antero-posterior fibres of this muscle draw forward the posterior part of the ciliary body and the anterior part of the choroid with the hyaloid membrane. This relaxes the suspensory ligament, and it in turn relaxes the lens capsule, hence the plastic lens bulges forward. At the same time the pull of the ciliary muscle exerts some pressure on the peripheral part of the vitreous, which must in its turn press upon the peripheral portions of the posterior surface of the lens. Simultaneously the circular fibres of the ciliary muscle tend to squeeze the marginal free portions of the crystalline lens in a circular manner, and therefore force the anterior surface forwards. The posterior surface of the lens is well supported by the jelly-like vitreous, and consequently it cannot bulge. Both these sets of fibres, the antero-posterior fibres and the circular fibres, are innervated by the third nerve.

3. *The Axes of the Eyeballs are directed inwards* by the associated movement of the internal recti muscles; these too are innervated by the third nerve.

From this it is seen that the third nerve conducts from the brain the efferent nervous impulses which supply the muscles involved in the act of accommodation.

Presbyopia.—After the age of forty to forty-five there appears, as a rule, some slight imperfection of accommodation, partly due to a slight loss of plasticity of the lens, and partly to some atonicity of the ciliary muscle. If the individual is emmetropic, parallel rays from infinity are brought to a focus upon the retina, consequently the individual can see distant objects quite well, but the presbyopic person finds difficulty in accommodating, the consequence of which is that he holds the page of print away from the eyes farther than the usual reading distance of 10 inches. In order to remedy this defect, a biconvex, convergent, or + glass is necessary for focussing near objects.

Ametropia.—In contradistinction to emmetropia is the condition of ametropia (ἀ, primitive, μέτρον, measure; not according to measure), which includes hypermetropia and myopia.

Hypermetropia.—The hypermetropic eye is one in which the antero-posterior axis of the eyeball is shorter than normal; parallel rays are therefore brought to a focus behind the retina. In order that they may be focussed upon the retina, a slight amount of action of the ciliary muscles must take place; in other words, a hypermetropic individual must accommodate slightly for distant objects, and consequently over-accommodate for near objects. This defect may be remedied by the use of weak biconvex, convergent, or + lenses, which should be habitually worn.

Myopia.—The myopic eye is one in which the antero-posterior axis of the eye is too long, the bulge in the eyeball usually occurs at the back. Parallel rays are brought to a focus in front of the retina, the myopic individual therefore fails to see clearly distant objects, but is usually able to see those near at hand, hence the term "short-sighted." He can see objects at a distance better if he screws up his eyes, this is because he makes a narrower slit to look through. The term myopia arose from this peculiarity (*μύειν*, to shut; ὤψ, the eye). The defect may be remedied by the habitual use of a biconcave, divergent, or a — lens; that is, a lens which causes the parallel rays of light to diverge before they become converged by the cornea and crystalline lens, and consequently are brought to a focus on the retina.

Astigmatism.—By regular astigmatism is meant that the amount of curvature of the cornea is unequal in any two meridians at right angles to one another; that is, the cornea may be more curved from above downwards than it is in a horizontal direction, or *vice versa.* The commonest form of regular astigmatism is that in which the vertical meridian of the cornea is more curved than the horizontal; this is known as the regular astigmatism "according to the rule." Sometimes the reverse condition occurs; this is astigmatism "against the rule." A similar condition may exist in any oblique meridian of the cornea. Regular astigmatism is remedied by the use of lenses unequally bevelled in two meridians at right angles to one another; these are cylindrical lenses. Irregular astigmatism is due to a local flattening of the cornea, and is incapable of being remedied by cylindrical glasses.

Lenses.

There are two chief varieties of lenses used for correcting errors of refraction, namely, *spherical* and *cylindrical.* Presbyopia and hypermetropia are corrected by the use of appropriate convex or + lenses, myopia by the use of concave or — lenses, and astigmatism by the use of + or — cylindrical lenses. For ophthalmic purposes a lens with a focal distance of 1 metre is taken as a standard. Such a lens has a refractive power of 1 dioptre, or 1 D. A lens with a focal length of ½ metre has a refractive power of 2 dioptres, or 2 D. A lens with a focal length of ⅓ metre has a refractive power of 3 dioptres, or 3 D, and so on.

Retinoscopy or Skiascopy.

This is known as the shadow test, and is an accurate means of estimating the condition of an individual's refraction. The test depends upon the fact that when light is reflected from a mirror into an individual's eye, the direction in which the light appears to travel across the pupil varies with the condition of the refraction of the eye. In performing the shadow test, the pupils of the "observed" (patient) should be previously dilated by means of a mydriatic. The patient is placed in a dark room with a light just above and behind his head. He must wear a trial spectacle frame to carry the lenses. The observer sits in front of and 1 metre away from the observed. Each eye must be examined separately. The observer, by means of a concave mirror, which has a hole in the centre, reflects light into the eye of the observed, and then slowly tilts the mirror from one side to the other. A shadow appearing in front of the red choroidal reflex is seen; the direction in which it moves is then noted. If the shadow moves *against* the direction of the tilted mirror the observed may be either emmetropic, in which case a + 1 D lens in the trial frame will neutralise the shadow, or hypermetropic, when the shadow will be neutralised by a higher + lens than a + 1 D.

If, when using a concave mirror, the observer finds that the shadow moves in the *same direction* as the tilted mirror, the observed is myopic, and a — 1 D is placed in the trial frame, higher — lenses are then employed until the movement of the shadow is neutralised. It is usual to add — 1 D to the strength of the lens which completely neutralises the shadow; this estimates the amount of hypermetropia, or myopia, as the case may be. Briefly, the following is an example: Concave mirror used, shadow moves in the *opposite* direction to the mirror, therefore the observed is emmetropic or hypermetropic. The point of reversal, *i.e.* the point at which there is no shadow, is obtained by using + 4 D, the observed is hypermetropic + 3 D (+ 4 D − 1 D). If, in similar circumstances, the shadow moves in the same direction as the rotation of the mirror, the observed is myopic. Suppose that the point of reversal is obtained with a − 2 D, the observed has − 3 D myopia (− 2 D − 1 D).

If, however, a *plane mirror* is used, the shadow moves in the *same direction* as the rotation of the mirror in emmetropia and hypermetropia, and in the *opposite direction* in myopia; but the direction of the shadow is neutralised in precisely the same way, as described above.

CHAPTER LI.

THE NEUROLOGY OF VISION.

THE RETINA.

STRUCTURE OF THE RETINA.

THE retina is the nerve layer in the posterior portion of the eyeball lying between the hyaloid membrane and the vascular choroid. Strictly speaking, it is an outgrowth from the brain, and should therefore be considered as a specialised part of the brain. It is made up of the following parts :—

1. On the outside, that is, against the choroid, is the layer of **pigment cells** ; these, when viewed on the surface, appear as six-sided or sometimes five-sided closely packed cells. The pigment consists of fine brown particles. These cells have elongated processes which contain pigment, and which dip down between the rods and cones of the next layer.

2. This is a **specialised nerve-epithelium**, and contains the following parts :—

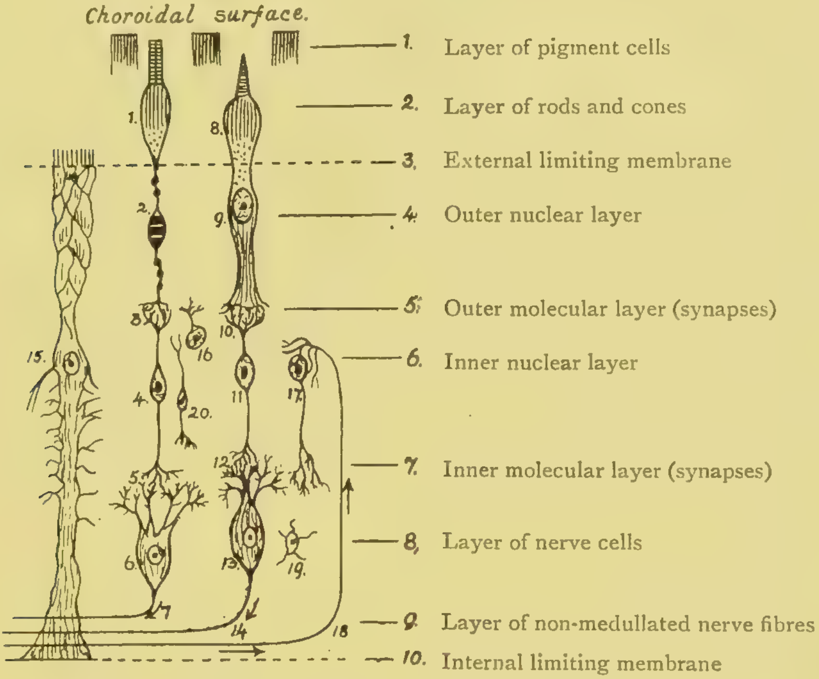
(*a*) *The Rods and the Rod Fibres.*—Each rod consists of an outer portion, elongated, and rounded something like the handle of a bat; it has transverse striations and three longitudinal grooves. Amongst the striations are fine pigment granules constituting the visual purple. These granules may be fixed with the vapour of 1 per cent. osmic acid solution. The innermost part of the rod is somewhat spread out, like the blade of a bat; the outermost portion of this part is longitudinally striated, something like a very wide splice, the innermost portion is distinctly granular, representing more or less the pegs put into a well-used bat. These granules stain with logwood. The base of the rod perforates the *external limiting membrane*, which is produced by the outer portion of the supporting fibres of Müller. The rod then continues into a body called the rod fibre. This fine fibre has a central oval nucleus with two or three transverse striations. The cell processes from the nucleus are finely varicose, the outer process continues into the base of the rod, the inner process runs into the outer molecular layer of the retina, where it forms a synapse.

(*b*) *The Cones and the Cone Fibres.*—The cones consist of an outer portion, small and somewhat pointed, transversely striated, but containing no visual purple. The innermost part of the cone is much widened out; its outer part is longitudinally striated; its innermost portion is slightly granular, and this part in marsupials and birds contains fine coloured fatty-like globules called chromophanes (this pigment is not responsive to light). The bases of the cones pierce the *external limiting membrane*, and continue as cone fibres in the outer nuclei layer of the retina. The protoplasm of the cone fibre is longitudinally striated, and in the centre is an oval nucleus which contains a round nucleolus. As already stated, the *external limiting membrane* is made up of the outer expanded portions of the sustentacular fibres of Müller; the main function of this membrane is to support the rods and the cones, and from it there are very fine hair-like processes which project externally between the rods and the cones. The *external nuclear layer* of the retina contains the rod fibres with their striated nuclei, the cone fibres with their nuclei, and the fine fibrils belonging to the supporting fibres of Müller. The pigment cell layer of the retina and the highly specialised nerve-epithelium (rods and rod fibres, cones and cone fibres) are nourished by the chorio-capillaris layer of the choroid.

3. **The Outer Molecular Layer** is finely fibrillated, and contains a few stellate cells, probably of neuroglial origin, and it also contains a number of synapses between the rod fibres and the rod bipolar cells, and also between the cone fibres and the cone bipolar cells.

4. **The Inner Nuclear Layer** mainly consists of rod and cone bipolar cells which form the first neurone on the visual path. These nucleated cells are bipolar; one process runs into the outer molecular layer and forms synapses with rod fibres, or with the cone fibres, and the inner process runs into the inner molecular layer, where it arborises around the peripheral processes of the ganglion cells. Besides the rod

and cone bipolars there are in this layer the nuclei of the supporting fibres of Müller. There are also cells called spongioblasts, which are oval and nucleated, and which give rise to a single process running inwards to the internal molecular layer. Arborising around these spongioblasts are


Choroidal surface.
1. Layer of pigment cells
2. Layer of rods and cones
3. External limiting membrane
4. Outer nuclear layer
5. Outer molecular layer (synapses)
6. Inner nuclear layer
7. Inner molecular layer (synapses)
8. Layer of nerve cells
9. Layer of non-medullated nerve fibres
10. Internal limiting membrane
1.
8.
2.
9.
3
10.
16
15.
4.
20.
11
17.
12
5.
6.
13.
19.
7
14
18

[Position of vitreous humour surrounded by the hyaloid membrane.]

FIG. 114.—Diagram to represent the structure of the retina.

1=Rod.
2=Rod fibre with transversely striated nucleus.
3=Synapse in the outer molecular layer.
4=Rod bipolar cell (first neurone).
5=Synapse in the inner molecular layer.
6=Ganglion cell (second neurone).
7=Afferent nerve fibre.
8=Cone.
9=Cone fibre with oval nucleus.
10=Synapse in the outer molecular layer.
11=Cone bipolar (first neurone).
12=Synapse in the inner molecular layer.
13=Ganglion cell (second neurone).
14=Afferent nerve fibre.
15=Sustentacular fibre of Müller, forming the outer (3) and inner (10) limiting membranes.
16=Amacrine cell.
17=Spongioblast.
18=Efferent nerve fibre.
19=Neuroglial cell.
20=Small bipolar cell.

non-medullated nerve fibres which have traversed the nerve fibre layer of the retina and arrived at the internal nuclear layer. There are also cells present called amacrine cells; these are small nucleated cells with a single short process which runs into the outer molecular layer. In addition a few small bipolar nerve cells are present in this layer. Ramifying between these various cells there is a fine capillary network derived from the central artery of the retina.

5. **The Inner Molecular Layer** of the retina contains many neuroglial cells, and numerous synapses between the rod and cone bipolars and the arborisations of the ganglion cells.

6. **The Layer of Ganglion Cells.**—These are flask-shaped cells with a single process running inwards, and many branching processes running outwards to the inner molecular layer. At the macula lutea these ganglion cells become more definitely bipolar, and are set somewhat obliquely two or three deep. By this arrangement the cones and cone fibres, which are found most abundantly in this area, are each connected with one ganglion cell by a single cone bipolar; whereas, in the surrounding part of the retina, each individual ganglion cell is connected with a number of rods and cones. It is said that in the more peripheral portion of the retina there may be as many as one hundred rods indirectly connected with a single ganglion cell. In the layer of ganglion cells there is a fine capillary network derived from the central artery of the retina. These ganglion cells form the second set of neurones.

7. Internal to the layer of nerve cells is the layer of **non-medullated nerve fibres.** These are mainly derived from the ganglion cells and are afferent in function, but there are some, however, of which the function is efferent.

8. The innermost layer of the retina consists of the **internal limiting membrane,** which is produced by the expanded bases of the sustentacular fibres of Müller; these fibres correspond with neuroglial cells. They lie in the retina, support the delicate structures there, and practically form the internal and external limiting membranes.

The retina has not the same structure throughout. In the peripheral portion the rods and rod fibres are most numerous, and, as already stated, there may be as many as one hundred rods connected up with a single ganglion cell; and this is brought about by the rod bipolar cells, and the arborisations which the ganglion cells make. The middle portion of the retina contains both rods and cones, and the ganglion cells are connected with fewer of these structures. The most receptive part of the retina is the *macula lutea*, or yellow spot of Sömmering, with its slightly depressed centre called the fovea centralis. Here the specialised nerve-epithelium mainly

PLATE I.

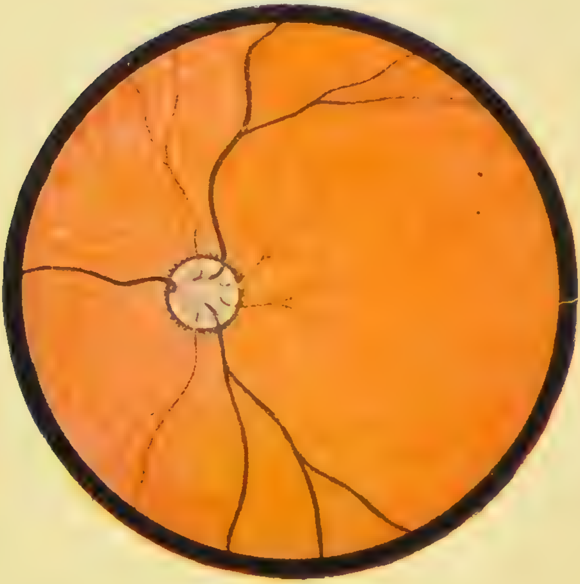


FIG. 115.—Fundus oculi. (*After* Mayou.)

The optic disc is seen with branches of the retinal artery and vein. On the macular side (outer side) of the disc are two small macular arteries.

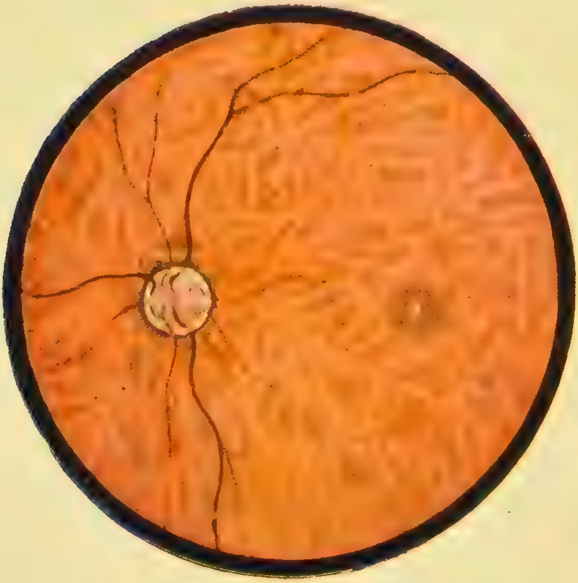


FIG. 116.—Fundus oculi. (*After* Mayou.)

The small white spot in the figure represents the fovea centralis of the macula lutea.

[*To face page* 663.

consists of long and slender cones with cone fibres, but there are in all probability also a few rods with their rod fibres present. At the actual fovea centralis the layers of the retina are somewhat thinned and spread out, but around the fovea the margins are somewhat thickened, and here the bipolar and obliquely set ganglion cells are four or five layers deep. Here, too, each elongated cone has its own cone bipolar, and its own ganglion cell, *e.g.* this portion of the retina is individualistic. In this region the fibres of Müller are set obliquely. The *blind spot* in the retina is situated on the nasal side, and is where the optic nerve enters the eyeball. Here the non-medullated nerve fibres, derived from the ganglion cells, pierce the lamina cribrosa, and acquire a medullated sheath. At this portion of the retina the nerve fibre layer alone is represented. The blind spot is perforated by the central artery of the retina and the central retinal vein, and is known as the optic disc (*vide* Fig. 115). Examined with the ophthalmoscope, the optic disc is seen as a well-defined circular pink body on a red background perforated by the central artery and vein of the retina. It is about 1·5 mm. in diameter.

The macula lutea is situated 3 mm. to the temporal side of the edge of the optic disc. It is difficult to see without having the pupil dilated by a mydriatic, since bright light, focussed on this the most responsive part of the retina, causes the pupil to contract at once. The macula is a circular area of deep red colour, due to the thin retina of this region allowing the vessels of the chorio-capillaris layer of the choroid to be more clearly observed (*vide* Fig. 116).

The Effects of Light falling on the Retina.

1. There is a certain amount of movement in the pigment cells of the retina whereby the melanin (fuscin) granules pass from the bodies of the pigment cells into the processes which lie between the outer portions of the rods and the cones.

2. The visual purple, or rhodopsin, which exists in the outer portions of the rods, and which is most probably derived from the melanin or fuscin of the pigment cells, is bleached.

3. The cones, and also possibly the rods, become somewhat more elongated.

4. There is a variation of the natural electrical currents of the retina, which indicates that chemical changes are taking place. It is found, when the eye is at rest,—that is, when it is not stimulated by light or in any other way,—that electrical currents pass from the cornea to the fundus oculi; that is, they are ingoing currents. The electrical conditions may be demonstrated by carefully excising an animal's eye, and placing one non-polarisable electrode on the cornea and the other at the back of the eye. The electrodes are then led off to a galvanometer or capillary electrometer.

If light rays fall upon the retina, electrical currents are produced which travel from behind forwards, *i.e.* the currents are outgoing. If the light rays are shut off there is a momentary increase of the outgoing current, but the eye *slowly* returns to its former electrical condition of rest. The electrical response of the eye to non-luminous, *e.g.* electrical, stimuli, lasts a considerable time, and the response is *always* an outgoing current. The current so produced is called the "blaze current." These currents of action are chiefly of retinal origin.

The Optic Nerve.

The optic nerve is an outgrowth from the brain, and therefore, strictly speaking, is not a cranial nerve, but part of the brain. It is surrounded by a layer of fibrous tissue derived from the dura mater; within this layer is the vaginal or lymph space, which is continuous with the sub-dural space. Internal to this is a layer of pia mater which surrounds the optic nerve. The optic nerve itself consists of medullated nerve fibres, and, as it is a portion of the white matter of the brain, these fibres have no primitive sheath. Between the fibres are neuroglial cells and a little connective tissue, but there are no distinct bundles of fibres such as are present in a nerve like the vagus. If a transverse section is made of the optic nerve immediately behind the eyeball, the central artery and vein of the retina may be seen in the middle of the nerve lying side by side. These are surrounded by a central lymph space. The optic nerve has some fibres which convey impulses from the retina (centripetal) to the brain, and others which convey impulses from the brain (centrifugal) to the retina. After division of the optic nerve some nerve fibres degenerate between the section and the eyeball, and other nerve fibres degenerate between the section and the brain. If one optic nerve is cut some nerve degeneration is found in the opposite optic nerve, suggesting that there are nerve fibres arising in the nerve cells of one retina, which travel back along the optic nerve, cross at the optic commissure, and travel down the opposite optic nerve to the retina (inter-retinal fibres). Generally speaking, the fibres derived from the peripheral portions of the retina enter the central part of the optic nerve, and the fibres derived from the central portions of the retina traverse the peripheral part of the optic nerve. The fibres derived from the macular region form the papillo-macular bundle, and at first pass in the outer portion of the optic nerve in a triangular area for a short way only, and then they gradually take up a more central position.

Deep Connections of the Optic Nerve.—Posteriorly the optic nerves are connected with the optic chiasma, and this in its turn is connected with the optic tracts. Each optic tract divides posteriorly into two main portions, the mesial or smaller portion is connected with the mesial corpus geniculatum and the posterior corpus quadrigeminum. So far as is known, this connection has nothing to do with vision. The lateral or larger portion of the optic tract contains the visual fibres, and makes three deep connections in the brain—

1. With the external corpus geniculatum.
2. With the pulvinar of the optic thalamus.
3. With the anterior corpus quadrigeminum or superior colliculus.

The nerve fibres which come from the temporal half of the retina, traverse the optic nerve on its outer side, and travel back through the optic tract of the same side, and make the deep connections as mentioned above. The fibres from the nasal half of the retina traverse the optic nerve on its innermost aspect; they travel back to the optic chiasma, where they cross to the opposite optic tract and make the deep connections as previously mentioned. That is to say, the fibres from the temporal half of each retina go to the same side of the brain, but the fibres which arise on the nasal aspects of the retinæ decussate in the optic chiasma. The fibres which come from the macular regions, and form the papillo-macular bundles, finally take up a central position in each optic nerve; some go to the optic tract of the same side on which they arise, and others cross at the optic chiasma.

These papillo-macular fibres go to both external corpora geniculata (*vide* Fig. 117). It will be seen from this that the fibres which arise in the macular regions of the retinæ are as far as possible equally bilaterally represented in the external corpora geniculata. The fibres which go to the external corpus geniculatum, to the pulvinar of the optic thalamus, and to the anterior corpus quadrigeminum, arborise in these regions around nerve cells. That is to say, these bodies are cell stations, and the cells in the external corpus geniculatum and in the pulvinar of the optic thalamus give rise to new fibres, which traverse the optic radiation of Gratiolet, which is in the posterior portion of the internal capsule of the corpus striatum, and go thence through the corona radiata to the grey matter

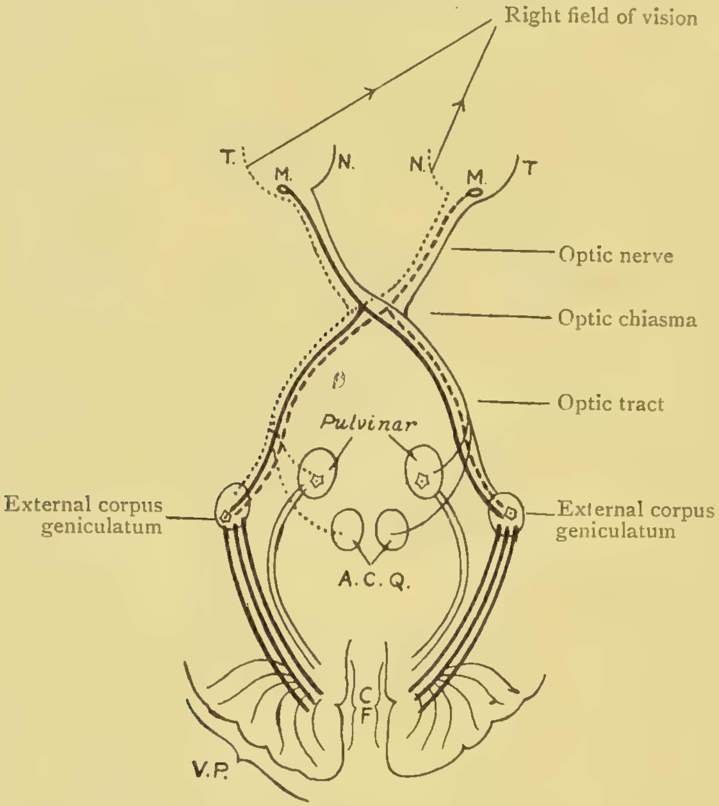


FIG. 117.—Diagram of the afferent visual paths from the retinæ to the brain.

A.C.Q. = Anterior corpora quadrigemina.
C.F. = Calcarine fissure, with the receptive visuo-sensory area.
V.P. = Occipital cortex (visuo-psychic area = associational area).
T. = Temporal half of retinæ.
N. = Nasal half of retinæ.
M. = Macular regions.

around the calcarine fissure, which is situated on the mesial aspect of the occipital lobe of the brain. This area of the brain is known as the visuo-sensory area. In the visuo-sensory area of the brain, which is the projection centre for visual impressions, the middle cell lamina of granules appears to be split by a thick band of nerve fibres. The outer layer of granules is really an addition to this region; the inner layer of granules is the hypertrophied true middle cell lamina or third layer of the grey matter. The thick band of nerve fibres referred to is the "line of Gennari"; scattered amongst these fibres are a few solitary cells of Meynert. This line consists of fibres, which belong to the third visual neurone, and arise in cells in the external corpus geniculatum and the pulvinar of the optic thalamus; and, as previously stated, travel through the optic radiation and corona radiata to the visuo-sensory area. It should be noted, then, that each macular region, through the external corpus geniculatum, is represented in each occipital lobe of the brain, so that a lesion of one occipital lobe will not abolish central vision in either retina.

The grey matter around the upper part of the calcarine fissure represents the upper quadrants of the retinæ, and the grey matter round the lower portion of the calcarine fissure represents the lower quadrants of the retinæ. The grey matter of the mesial aspect of the occipital lobe of the brain, apart from that which is in the immediate vicinity of the calcarine fissure, and the grey matter of the external portion of the occipital lobe, form the visuo-psychic area. Flechsig suggests that the fibres from the external corpus geniculatum are those which end exclusively in the neighbourhood of the calcarine fissure, and that therefore the grey matter around the calcarine fissure represents the macular regions. It will be seen, then, that on the visual tract there are three neurones,—the first neurone is in the internal nuclear layer of the retina, and consists of the rod or the cone bipolar cell; the second neurone is the ganglion cell of the retina, and its projection fibre; the third neurone commences in the external corpus geniculatum and the pulvinar of the optic thalamus, and ends in the middle cell lamina of the cortex cerebri, forming the line of Gennari, which is characteristic of the grey matter around the calcarine fissure. It is stated that 80 per cent. of the fibres of the optic tract go to the external corpus geniculatum, and with regard to vision, therefore, the third neurone which commences here is the most important. The connection of the optic tract with the anterior corpus quadrigeminum is probably to bring the tract into relationship with the third nerve nucleus which lies immediately underneath it, and the connections of the optic tract, with the posterior corpus quadrigeminum, are probably of use in connecting up the tract with the nuclei of the third, fourth, and sixth cranial nerves. The three nuclei of the third, fourth, and sixth cranial nerves are connected together by fibres contained in the posterior longitudinal bundle. Through this bundle, by some fibres from it which cross the middle line, the nucleus of the sixth nerve of one side is connected with that part of the opposite third nerve nucleus which supplies the internal rectus muscle. It is possible that one function of the corpora quadrigemina is to exercise some co-ordinating influence over the nuclei which give rise to fibres which supply the eye muscles. Lesions in the neighbourhood of the corpora quadrigemina are associated with a certain amount of inco-ordination of the movements of the eyeballs called nystagmus. The co-ordinating function of the corpora quadrigemina is governed, however, by the highest co-ordinating centre, the cerebellum.

If the optic tract is cut, nerve degeneration takes place between the section and the deep connections; this suggests that the fibres which degenerate are cut off from their trophic nerve cells in the retina. These fibres are centripetal. Degeneration also takes place between the section and the eyeball; this suggests that the fibres which degenerate have trophic nerve cells somewhere in the deep connections of the optic tract. These fibres are centrifugal. There are therefore in all probability fibres which come from nerve cells in the external corpus geniculatum, in the pulvinar of the optic thalamus, and in the anterior corpus quadrigeminum, which traverse the optic tract, the optic chiasma, and the optic nerves, and end by arborising around nerve cells in the internal nuclear layer of the retinæ. It may be that the function of these impulses is to control the chemical changes which occur in the cells of the retina. It has been already stated that if one optic nerve is cut, some fibres undergo degeneration between the section and the deep connections of the nerve, and that other fibres degenerate between the section and the eyeball. There are other fibres, however, which degenerate between the cut back to the optic chiasma and down the other optic nerve. These are inter-retinal fibres, which are probably collaterals from the second visual neurone; they cross in the optic chiasma, and travel down the opposite optic nerve and arborise around cells in the retina.

Lesions of the Visual Tract.—1. Section of the optic nerve causes total blindness in that eye.

2. Section through the optic chiasma causes blindness in the nasal halves of the retinæ, and therefore causes blindness in both of the outer portions of the fields of vision (bi-temporal hemianopia). This lesion sometimes occurs when the optic chiasma is pressed upon by tumours of the pituitary body, and also occurs in some advanced cases of acromegaly.

3. A lesion of the optic tract causes blindness in the temporal half of the retina of the same side, and blindness in the nasal half of the retina of the opposite side; this results in blindness in the field of vision opposite to the optic tract involved, *i.e.* if the left optic tract is involved, there is, as a result, right hemianopia. In other words, the individual has left hemiopia,—that is, his left field of vision is intact. If, in such a case as this, rays of light are allowed to fall on the temporal half of the left retina and on the nasal half of the right retina, the pupils will not react to light, because there is a lesion of the light-reflex arc in the optic tract. This is called Wernicke's pupillary inaction.

4. A lesion involving the optic radiation in the internal capsule of the corpus striatum results in opposite hemianopia; *i.e.* if the lesion is in the left internal capsule there will be right hemianopia; if, however, rays of light are allowed to fall on either the temporal half of the left retina or the nasal half of the right retina, the pupils will react to light, because the lesion is behind the reflex arc, that is, the direct light reflex is present. Such a lesion as this is usually associated with opposite hemiplegia, and sometimes with hemianæsthesia, because the motor and sensory fibres which traverse the internal capsule are also usually involved. That is to say, a complete lesion of the internal capsule on the left side of the brain results in right hemiplegia, right hemianæsthesia, and right hemianopia, and *vice versa* for a complete lesion of the right internal capsule.

5. A lesion involving the brain substance around the calcarine fissure and the adjacent part of the occipital

cortex produces opposite hemianopia. The pupillary light reflex is present, but there is no hemiplegia nor hemianæsthesia. In man the grey matter in the angular gyrus is the visual word centre, and a lesion in this neighbourhood on the left side of the brain, in a right-handed individual, produces "word blindness," *i.e.* an individual will see words but will be unable to appreciate their meaning; this is one variety of sensory aphasia.

It has been pointed out that the chief function of the grey matter of the outer surface of the occipital lobe is visuo-psychic, or the association area for images perceived, *i.e.* the area for visual memory. The faculty of orientation is therefore located in this region. Hence, if an individual becomes blind through disease of the eyes or the optic nerves, the faculty of orientation is still present, consequently he is able, to a certain extent, to find his way about; whereas, if both occipital lobes are completely injured or diseased, this faculty is lost.

THE NEURO-MUSCULAR MECHANISM OF THE EYEBALL.

The eyeballs move smoothly in various directions within the capsule of Tenon, which contains some unstriped muscle fibres, innervated through the cervical sympathetic.

Fig. 118 represents the position of attachment of the muscles into the eyeball, and the arrows indicate the direction of the movements produced by their action.

Every movement of the eyeball is a synkinesis.

Complete adversion is produced by the combined action of the internal, superior, and inferior recti, at the same time the antagonistic muscles are actively inhibited.

Complete abversion is brought about by the combined action of the external rectus, superior, and inferior obliques. Movement directly upwards is due to the combined action of the superior rectus and inferior oblique; movement directly downwards is due to the inferior rectus and superior oblique muscles acting together. In normal circumstances, there is always binocular synkinesis, abversion of one eye is accompanied by adversion of the other; this is conjugate deviation.

Elevation of the two eyes occurs at the same time, likewise also depression.

Bilateral adversion of the eyes, however, occurs in accommodation, and with this inward movement of the eyeballs the pupils contract.

Elevation of the eyes is usually accompanied by some slight abversion, and depression by some slight adversion.

Nuclei of Nerves innervating Eye Muscles.

The third nerve nucleus consists of groups of cells situated alongside the aqueduct of Sylvius, and beneath the anterior corpus quadrigeminum. Some of the fibres of the third nerve cross the middle line and emerge with the third nerve of the opposite side. From before backwards the following muscles are represented in these groups of nerve cells :—

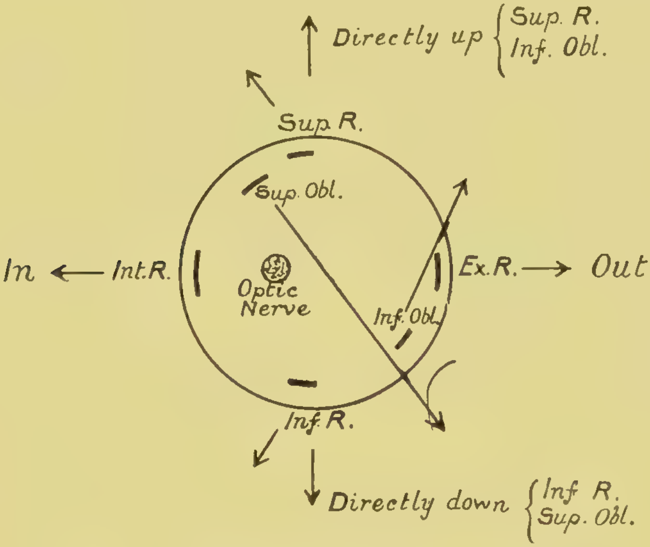


FIG. 118.—Right eyeball viewed from behind.

Muscle.	Movement.
Internal rectus.	Adversion or inversion.
External rectus.	Abversion or eversion.
Superior rectus.	Upwards and inwards.
Inferior rectus.	Downwards and inwards.
Superior oblique.	Downwards and outwards.
Inferior oblique.	Upwards and outwards.

Sphincter pupillæ and ciliary muscle.—The cells comprising this part of the nucleus are small and situated near the middle line; "they, with the cells of the opposite side, form an unpaired nucleus with two divergent horn-like processes in front (the Edinger-Westphal nuclei)."

Levator palpebræ superioris.
Superior rectus and inferior oblique.
Internal rectus.
Inferior rectus.

The fourth nerve nucleus is situated alongside the aqueduct of Sylvius, and beneath the posterior corpus quadrigeminum; this innervates the *superior oblique*. The fibres from the fourth nerve nucleus pass backwards and downwards and decussate with those of the opposite side.

The sixth nerve nucleus is situated in the foremost part of the floor of the fourth ventricle; it innervates the *external rectus* muscle of the same side, and gives rise to some fibres which cross the middle line and connect up with those cells in the opposite third nerve nucleus, which innervate the opposite internal rectus muscle (*vide* p. 535). If the right sixth nerve nucleus is stimulated it causes the right external muscle to contract, and at the same time the *left* internal rectus muscle contracts; the result of this is that the eyes turn to the right, *i.e.* there is conjugate deviation of the eyes to the side of stimulation.

It will be observed that the nuclei of the nerves which innervate the eye muscles are physiologically associated thus:—

Upward movement.	*Levator palpebræ superioris.* *Superior rectus and inferior oblique.*
Inward movement.	*Internal rectus.*
Downward movement.	*Inferior rectus.* *Superior oblique.*
Outward movement.	*External rectus.*

Behind and also between the sixth nerve nuclei is situated the seventh nerve nucleus, fibres from which course round the more superficial sixth nerve nucleus, so that lesions of the sixth nerve nucleus are usually accompanied by facial nerve paralysis (*vide* p. 530).

Signs of Paralysis of the Nerves which supply the Eye Muscles.

Paralysis of the third nerve causes *ptosis*, or drooping of the upper eyelid, due to paralysis of the levator palpebræ superioris. If the lid is raised the eyeball is observed to be abverted (*external strabismus*); this is due to paralysis of the internal rectus muscle, and to over-action of the external rectus. The eyeball is also deflected slightly downwards, owing to the unopposed action of the superior oblique. There is impairment of the movements of the eyeball. The eyeball cannot be turned up because of paralysis of the superior rectus and inferior oblique muscles; the eye cannot be adverted because of paralysis of the internal rectus muscle, nor can it be turned directly down because of paralysis of the inferior rectus muscle. The pupil is dilated (*paralytic mydriasis*); this is due to paralysis of the sphincter pupillæ. The ciliary muscle is paralysed, so that accommodation is impossible. The individual complains of seeing double (*diplopia*), the false image is on the sound eye side of the true image; this is crossed diplopia. When the fourth nerve is paralysed the individual is incapable of rolling the eyeball downwards and outwards because of paralysis of the superior oblique muscle, nor can the eyeball be turned directly downwards. On attempting to look downwards the eyeball is rotated down and in; this is due to the unopposed action of the inferior rectus muscle. On looking down, therefore, there is some slight internal squint (*internal strabismus*), and the eyeball is slightly rotated; this causes diplopia. The false image is on the "squinting eye" side of the true image (*homonymous diplopia*), and the false image is oblique, due to rotation of the eyeball. If the sixth nerve is paralysed the external rectus muscle is involved. The eyeball is adverted (*internal strabismus*), and there is limitation of abversion. Diplopia occurs when the individual looks towards the side of paralysis; this is *homonymous diplopia*, the false image being on the same side as the squinting eye. The false image is erect.

If the sympathetic nerve in the neck becomes paralysed, the plain muscle in Tenon's capsule loses its tone, and the eyeball recedes slightly (*enophthalmos*). At the same time there is *slight ptosis*, or drooping of the upper lid, because of the paralysis of the plain muscle (Müller's muscle) which is present in the upper lid. In ordinary circumstances this muscle causes the eyelids to remain separate, and the eyes to remain open after the upper lid has been elevated by the levator palpebræ superioris. In consequence of sympathetic paralysis the pupil becomes contracted, due to over-action of the sphincter pupillæ through paralysis of the dilator pupillæ muscle.

If the upper or oral cut end of the sympathetic nerve in the neck is stimulated by a faradic current, *inter alia*, the palpebral fissure between the lids becomes widened, due to the contraction of Müller's muscle; the eyeball is slightly protruded (exophthalmos), because of the over-action of the plain muscle in Tenon's capsule, and the pupil becomes dilated, due to the over-action of the dilator pupillæ muscle.

Binocular Vision.

In each retina there is an area which is not responsive to light rays, this is the "blind spot," which corresponds with the position where the optic nerve enters the eyeball. These "blind" spots are situated on the nasal side of the maculæ, and, as the temporal half of one retina corresponds with the nasal half of the other, and *vice versa*, the "blind spots" are not corresponding parts of the retinæ, hence the presence of a blind spot is, in normal circumstances, not apparent. At the same time, it will be readily understood that the "blind spots" have no cortical representation in the visuo-sensory area of the brain.

A judgment of the height or breadth of an object is arrived at by the following considerations:—

1. The kinæsthetic sensations produced in the eye muscles as the eyes travel in the endeavour to view the object from foot to top and top to foot, if height is being estimated, and from side to side, if breadth is being estimated.

2. The size and clearness of the retinal image produced by the object.

3. Previous experience of such measurements (association of ideas). As a rule height is overestimated and breadth is underestimated.

In judging of the third dimension, or depth, the three factors mentioned above are called into play, and a fourth is added, namely, that the two retinal images obtained are not *quite* identical, as each eye views the object from a slightly different point of view; this is obvious when it is remembered that the eyes are a considerable distance apart. The two pictures thus obtained are then psychologically compared, and in this way a judgment is arrived at.

THE FUNCTIONS OF THE RETINA.

When the retina is stimulated by light, three distinct kinds of sensation are produced:—

1. Sensations of light.
2. Sensations of form.
3. Sensations of colour.

1. **Sensations of Light.**—The sensory nerve-epithelium in the retina is the part which is affected by light stimuli, and in accordance with the strength of the light stimuli the intensity of light sensations varies directly. One lighted candle in a dense room produces a sensation of brightness, two lighted candles produce double the sensation of brightness; four lighted candles, however, produces only three times the brightness sensation of one lighted candle. According to Weber's law, "Sameness of difference in sensation means *proportional* sameness of difference between stimuli." For light sensations the discriminative sensibility is $\frac{1}{100}$; that is, if a room is illuminated by one hundred candles and one more lighted candle is introduced there is *just* an increase in brightness sensation. If the room were illumined by one thousand candles, then ten more lighted candles must be introduced in order that an increased sensation of brightness may be produced.

2. **Sensations of Form.**—This particular function of the retina by which the shape of objects is perceived seems to be located in the cones and the cone fibres. Form sensation is most highly developed at the macula, and in this region of the retina the cones are highly differentiated and are massed together. Form sense gradually diminishes in the parts of the retina more removed from the macula, and is least developed in the extreme peripheral portions. This diminution of form sense agrees with the diminution in the number of cones. The term *acuity of vision* is used to indicate this power of distinguishing the shapes of objects, and this variety of vision is central or macular.

Visual Adaptation.—The central and peripheral portions of the retina differ from each other with regard to their responsiveness to external stimuli, *i.e.* central vision and peripheral vision differ from each other both in kind and in degree. The central portion of the retina responds to strong stimuli, *i.e.* bright light or light of long wave length; whereas the peripheral portion is characterised by an increased responsiveness to feeble stimuli, *i.e.* to light of moderate and short wave length; the peripheral portion is more susceptible to adaptive changes, for instance, the pupil dilates in the dark, the "dark-adapted" eye; whereas, if the retina is sensitive, the pupil contracts in the light, the "light-adapted" eye.

According to the Duplicity Theory of Parinaud and v. Kries, there are two distinct visual mechanisms in the retina.

1. *The one subserves Achromatic and Chromatic Responsiveness.*—This portion belongs to the more central part of the retina, and is probably especially connected with the cones, which are more numerous in this region of the retina. This mechanism is active in bright daylight, and is unaffected by resting in the dark. It should be noted that cones are particularly plentiful in the retinæ of most birds, and these have most useful vision in daylight; their retinæ are not readily adapted to twilight and dark, hence their period of rest commences with sundown.

2. *The other Mechanism especially subserves Achromatic Sensations.*—The part of the retina involved in this mechanism is particularly the rods and the visual purple which they contain. These are most plentiful in the peripheral portions of the retina, and are less abundant towards the macula. The rods seem to be the chief agency of vision in twilight, and are especially characterised by a responsiveness to ethereal vibrations of short wave lengths. The rods with their visual purple are, moreover, particularly abundant in the retinæ of those types of animals which have the twilight variety of vision, such as owls and bats.

According to Parinaud, in cases of hemeralopia or nyctalopia (night-blindness) the vision is of the macular type, the peripheral part of the retina is not responsive to stimuli. Colour sense, which is central in the retina, is normal, though the spectrum is shortened at the violet end, and the responsiveness to short waved light is low. Nyctalopia occurs in the disease known as pigmentary degeneration of the retina, the patients are unable to adapt the vision at twilight; hence the term twilight or night-blindness. There is probably some impaired function of the visual purple which exists in the rods. On the other hand, in cases of blindness from nicotine poisoning (tobacco amblyopia), the ganglion cells of the retina connected with the macular region (? cones), which are the most highly differentiated, are the earliest to degenerate as the result of the poison. Degeneration follows in the papillo-macular bundle. In this disease, therefore, it is the macula lutea which is early involved, the result of which is that there is loss of acuity of vision and impairment of colour sensation. There is also a central scotoma (blind spot) for both red and green.

Sensations of Colour.—Colour vision deals with colour sensations and not with pigments. By using the perimeter and mapping out the fields of vision for various external visual stimuli, it is found that practically the whole of the retina (with the exception of the blind spot) is responsive to the external stimuli black, grey, and white, and the sensations produced are called brightness sensations. Further, it is found that it is the macular region of the retina and the regions immediately adjacent which are particularly responsive to the colour stimuli, and this is that portion of the retina where the cones are most numerous. It is quite possible, therefore, that the cones and the cone fibres are immediately connected with colour sensations. Rays of light from an external object, which give rise to the sensation of white, appear to exert a certain amount of "spread of stimulus" in the retina; the result is that there is an increased amount of sensation. A white object on a dark background therefore appears larger than a black object of equal size on a white background; in other words, a white object always appears larger than it really is. This phenomena is termed *irradiation.*

The colour of a coloured object is not appreciated by the peripheral portions of the retina, but only by the more central portion where the cones are particularly numerous. Here too there are differences for different colours. The visual fields for red and for green, as mapped out with the perimeter, for instance, are smaller than those for yellow and blue.

THEORIES OF COLOUR VISION.

Ultra-red rays=heat	R	O	Y	G	B	I	V	*Ultra-violet rays*= chemical (actinic)

Red	Rays least bent by a prism. 394 billion vibrations per second. Long wave lengths.	*Violet*	Rays most bent by a prism. 762 billion vibrations per second. Short wave lengths.

FIG. 119.—Colours of the Spectrum.

There are two chief theories of colour vision :—

1. *The Theory of Young and Helmholtz, called by v. Kries the Three Components Hypothesis.*—Colour sensations depend upon the activity of three independent "physiological substances" of unknown nature situated in the retina. Each substance is selectively stimulated by the colour stimuli, red, green, and violet, and so produces the elementary colour sensations of such (*vide* Fig. 120). The sensations of the intermediate colours depend upon different strengths of stimulation of these physiological substances. The sensation of orange is produced by strong stimulation of the "red" substance, and some slighter stimulation of the "green" substance; the sensation of blue is due to strong stimulation of the "green" substance, and a less stimulation of the violet substance, etc. The sensation of white is produced by the three sets of physiological substances being equally stimulated by red, green, and violet, whereas the sensation of black is due to the absence of external light stimuli. It will be seen that this theory deals rather with stimulus relations than with sensations.

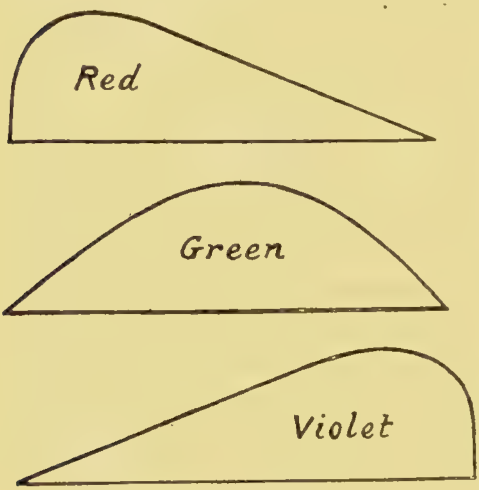


FIG. 120.

2. *The Theory of Hering.*—In the retina there are three sets of "visual substances," each of which is differently affected by light waves.

The three sets of visual substances are termed

The black-white substance ;
The green-red substance ; and
The blue-yellow substance.

If the external stimulus brings about anabolic changes in the black-white substance, the sensation produced is black ; if, on the other hand, the stimulus produces katabolic changes in the black-white substance, the resulting sensation is white. Again, if the external stimulus produces anabolic changes in the green-red substance, the resulting sensation produced is green, but if katabolic changes are excited in the same substance the resulting sensation is red, and the same holds good for the blue-yellow substance.

	Anabolic changes diminish the intensity of the sensation, *i.e.* negation, producing a sensation of	*Katabolic* changes increase the intensity of the sensation, *i.e.* action, producing a sensation of
Black-white substance .	Black	White
Green-red substance .	Green	Red
Blue-yellow substance .	Blue	Yellow

This theory deals rather with sensations than with stimuli. It is possible that the "black-white substance" is present all over the retina, and the sensations produced by the stimulation of this substance are not truly colour sensations but brightness sensations, and if there are two equal stimuli of black and white affecting the black-white substance the result is a sensation of grey, due probably to the continued activity of the cells in the retina. Every light affects the black-white substance, and therefore produces the sensations of brightness, namely, black, neutral grey, or white.

Brightness sensations are therefore present with colour sensations. If, therefore, equal stimuli of green and red affect the green-red substance, the colour sensations neutralise one another, but the resulting sensation is one of brightness, that usually present being the neutral grey sensation.

In cases of total colour blindness (achromatopsia) the colours of the spectrum appear as a band of light, and the sensations produced by the colours differ only in brightness. In some cases there is a central scotoma, or blind spot, suggesting that the fovea centralis is not responsive to light. This is the region in the retina where the cones predominate, and this fact rather suggests that the cones are associated with colour vision.

After-Images.

These are due to the after-effects of retinal stimulation, and are of two kinds: the *positive* and the *negative*.

Positive after-images resemble the original image in both brightness and colour; this phenomenon may be appreciated when a rapidly revolving carriage wheel is observed,—individual spokes are not seen, but appear to be fused. The sensation lasts longer than the stimulus which produced it, just as the sting lasts longer than the blow which excited it.

Negative after-images resemble the original image in form, but differ in brightness and in colour, less bright portions of the original image appear brighter in the negative after-image, and *vice versa.* If the original image produces a colour sensation, the negative after-image produces the complementary colour sensation. This phenomenon is more readily explained by the Hering theory of colour vision, thus: If the object seen is black it produces anabolic changes in the "black-white substance" of the retina, resulting in the sensation of an image which is black. After anabolism has taken place katabolism must occur, the result of which is that a negative after-image is produced with the resulting sensation of white. A similar explanation may be held to account for the colour sensations which occur from the negative after-images. The sensation of green (anabolic) is followed by the sensation of its complementary colour red (katabolic), the sensation of blue followed by the sensation of its complementary colour yellow.

Contrast.

There are two varieties of contrast to be described: *Successive contrast* and *simultaneous contrast.* The negative after-images just described are frequently spoken of as the phenomena of successive contrast.

Simultaneous contrast is applied to brightness sensations and colour sensations. Referring to the sensations of brightness, the phenomena may be stated as follows: A neutral-grey object appears less bright when viewed upon a white background than when viewed upon a black background.

Referring to the sensations of colour, the phenomena may be described as follows: A neutral-grey object, when surrounded by green, appears to acquire a tint of the colour complementary to green, namely, red. A neutral-grey object, when surrounded by blue, appears to acquire a tint of its complementary colour, namely, yellow. Simultaneous contrast persists in after-images; thus, if a grey strip, which acquires a red tint when surrounded by a green square, is looked at intently for one minute, and then the eye is directed to a surface of white paper, the grey strip will acquire a green tint, and appear to be surrounded by a red square. Simultaneous contrast is of sensory origin, and is more easily understood when Hering's theory of colour vision is applied to the phenomena.

THE EAR.

CHAPTER LII.

THE ORGAN OF HEARING.

The organ of hearing consists of three parts, namely, the external, the middle, and the internal ear, though, from a physiological point of view, it consists of—

1. The sound-conducting part, which includes the external, middle, and part of the internal ear.
2. The sound-perceiving part, which includes the organ of Corti, part of the auditory nerve, and the auditory centres in the brain.

The External Ear.

The external ear includes the auricle, or pinna, and the external auditory meatus.

The pinna consists of the following parts: The external rim, or helix, which ends below in the lobule. Internal to the helix is the fossa of the helix, or the scaphoid fossa. Internal to this is the anti-helix, which ends anteriorly and above in the fossa of the anti-helix, or the triangular fossa. Below and anterior, the anti-helix is continuous with the anti-tragus. The rounded depression in front of the anti-helix is the concha. Immediately in front of the concha is the tragus, which protects the external auditory meatus. The auricle is moved slightly backwards by the retrahens aurem muscle, upwards by the attollens aurem muscle, and anteriorly by the attrahens aurem muscle. These muscles are supplied by the facial nerve. In the lower types these muscles have considerable power over the movements of the pinna, but in man they have a very slight action only; the vestigial intrinsic auricular muscles are also supplied by the facial nerve. The pinna is made up of skin which contains sebaceous glands. Beneath the skin there is a fibrous perichondrium, which covers yellow elastic cartilage. This cartilage is continuous with the fibro-cartilage, which forms part of the external auditory meatus. The lobule of the ear consists of skin, fat, and fibrous tissue; there is no cartilage present. The main function of the pinna is to receive sound waves, and to reflect them down the external auditory canal. The

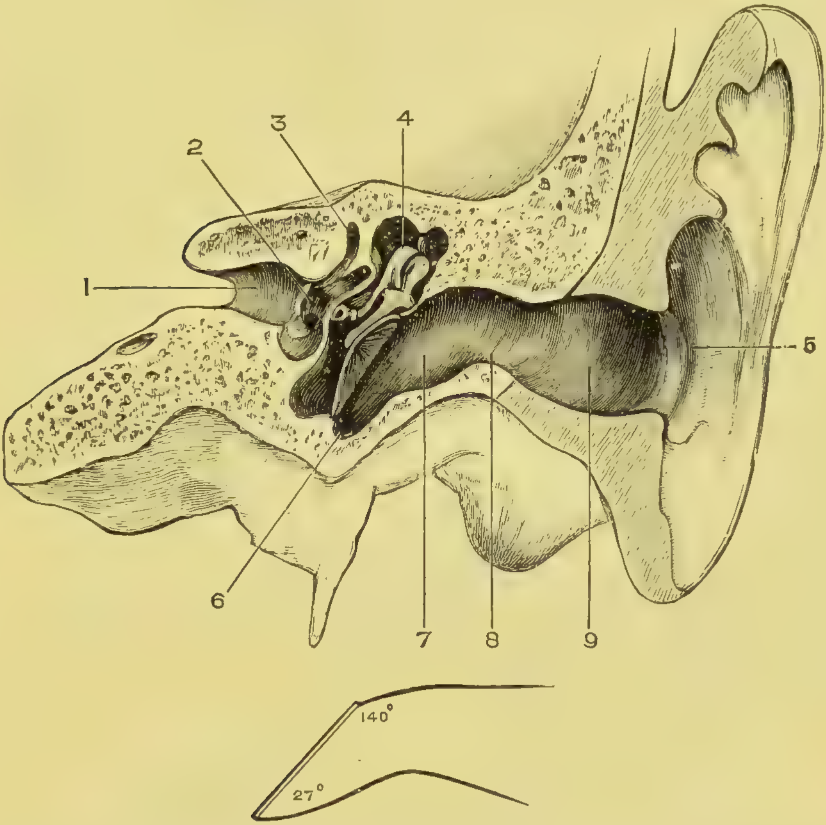


FIG. 121.—A vertical section through the ear—to show the external auditory canal, the tympanic cavity, and the internal ear. (Drawn from a preparation in the collection of Hunter Tod.)

1 = Internal auditory meatus.
2 = Labyrinth.
3 = Semicircular canal.
4 = Incus and malleus.
5 = Concha.
6 = Sinus of external meatus.
7 = Bony meatus.
8 = Narrowing of the meatus at the junction of the cartilaginous and bony portions.
9 = Cartilaginous meatus.

The lower figure represents the obliquely set membrana tympani, making an angle of 140° with the roof of the external auditory canal.

external auditory meatus continues on as the external auditory canal, which is about 1¼ inch long, the outer portion of which consists of fibro-cartilage, the inner portion is bony. The canal is lined with skin, which is intimately attached to the cartilage and to the periosteum of the bone. In the skin of the external auditory meatus and the canal are well-defined hairs and modified sweat glands. These ceruminous glands secrete the cerumen or wax. The function of the hairs is to keep out dirt particles, and whenever the lower jaw is elevated and depressed the hairs move slightly outwards. The use of the cerumen is partly to lubricate the hairs, and partly to moisten the membrana tympani, which is found at the bottom of the external auditory canal.

Function of the External Ear.—The auricle collects the vibrations of the air, or sound waves, and transmits them through the external auditory meatus to the external auditory canal, and these vibrations impinge upon the membrana tympani. This membrane is drawn inwards at its centre, but around the depression (umbo) it bulges slightly outwards. This somewhat trumpet-shaped membrane is unevenly, and not very tightly, stretched, the consequence of which is that the membrane can vibrate to a large range of tones; the range of tones to which it is able to vibrate is said to pass through seven octaves (Yearsley).

THE MIDDLE EAR, OR TYMPANUM.

The middle ear is a cavity about one-third of an inch from side to side. Its boundaries are as follows: The roof consists of a thin plate of bone, the tegmen tympani, which separates the middle ear from the cranial cavity. This is traversed by a few small veins. The floor consists of a thin plate of the temporal bone, which separates the middle ear from the jugular fossa, which contains the sinus of the jugular vein. In the floor is a foramen for the entrance of the nerve of Jacobson. The external wall is made up of a ring of bone, incomplete above (notch of Rivinus), called the annulus tympanicus, attached to which is the membrana tympani. This consists of three layers,—an external layer of stratified epithelium, which is derived from the external auditory canal; an innermost layer derived from the mucous membrane, which lines the middle ear; and a middle portion called the membrana propria. This consists of fibro-elastic tissue, of which some fibres are concentrically (internal) placed around the handle of the malleus, and some which radiate (external) from the centre of the membrana tympani. The membrana propria is traversed by fine capillaries. The membrana propria is not fully formed above, so that this portion of the membrana tympani consists mainly of a reflection from the external auditory canal and the middle ear. This part is known as the membrana flaccida of Shrapnell, and is bounded below by the anterior and posterior tympano-malleolar ligaments. The central portion of the membrana tympani is somewhat depressed inwards towards the middle ear. This

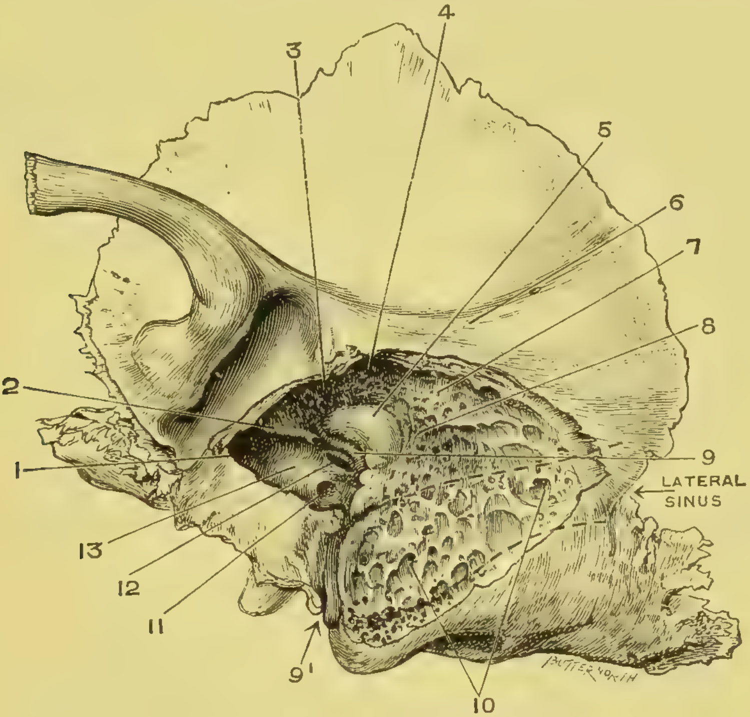


FIG. 122.—Diagram to show the position of the middle ear and its relation to the mastoid process. (From a preparation in Hunter Tod's collection.)

1 = Anterior wall of external auditory meatus partially removed.
2 = Canal for the tensor tympani muscle.
3 = Attic.
4 = Aditus.
5 = External semicircular canal.
6 = Posterior root of zygoma.
7 = Tegmen tympani.
8 = Antrum.
9 = Fallopian canal for the facial nerve.
9¹ = Stylo-mastoid foramen.
10 = Mastoid air cells.
11 = Fenestra rotunda.
12 = Fenestra ovalis.
13 = Promontory.

The dotted lines show the outline of the sigmoid groove for the lateral sinus.

depression is the *umbo*, and is attached to the tip of the handle of malleus. Crossing the membrana tympani on its inner aspect between the handle of the malleus and the long process of the incus is the chorda tympani nerve. The membrana tympani is set obliquely from above downwards and inwards, forming an angle of 140° with the roof of the external auditory canal (*vide* Fig. 121). The inner wall of the middle ear consists of part of the petrous portion of the temporal bone, and on it are the following structures. Near its centre is the promontory or tuber cochleæ, which juts out towards the middle ear, and is produced by the first turn of the cochlea. Ramifying in the mucous membrane, over the promontory, is the tympanic plexus of nerves, which is made up of the following communications:—

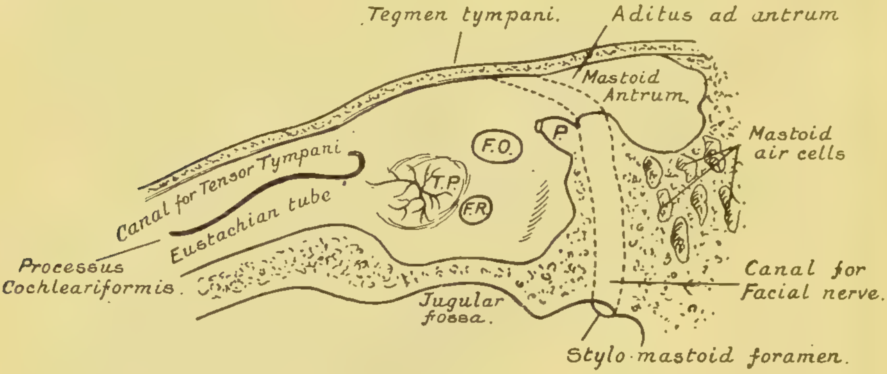


FIG. 123.—Diagram to represent the inner wall of the left middle ear.

P. = Pyramid containing the stapedius muscle.
T.P. = Promontory with grooves for the tympanic plexus.
F.O. = Fenestra ovalis.
F.R. = Fenestra rotunda.

1. The small deep petrosal nerve from the carotid plexus of sympathetics.
2. Tympanic branch from the glosso-pharyngeal (nerve of Jacobson).
3. A twig to the geniculate ganglion of the facial nerve.
4. The small superficial petrosal nerve which passes to the otic ganglion.

This plexus supplies:—

1. The mucous membrane of the tympanum.
2. The mucous membrane of the Eustachian tube.

It is most probably through Jacobson's nerve that the cranial impulses pass viâ the glosso-pharyngeal nerve, the tympanic plexus, the facial nerve, and the chorda tympani to the submaxillary and sublingual glands, and through the otic ganglion and the auriculo-temporal nerve to the parotid gland.

Just above and behind the promontory is an oval depression, the fenestra ovalis, the margin of which is covered in by a very thin layer of hyaline cartilage, against which fits the foot of the stapes. Behind and below the promontory is the fenestra rotunda, which is filled in by the secondary tympanic membrane. This has an outer covering derived from the mucous membrane of the middle ear, a middle elastic portion consisting of fibro-elastic tissue, and an inner covering derived from the lining of the scala tympani. In the superior angle of the inner wall is the aqueductus Fallopii, which transmits the facial nerve. The posterior wall of the middle ear consists of bone, which separates the middle ear from the mastoid process, which contains the mastoid antrum and mastoid air cells. Lying behind this plate of bone is the aqueductus Fallopii, which contains the facial nerve and stylo-mastoid artery. Jutting forwards and slightly upwards from this plate of bone is the pyramid, which contains the fibres of the stapedius muscle, the tendon of which comes through a small opening in the apex. This little muscle is supplied by the facial nerve. Just above the pyramid is that portion of the middle ear known as the attic, which posteriorly leads to the aditus, which opens through the back wall of the middle ear into the mastoid antrum or tympanic receptacle. The external landmark for the mastoid antrum is that triangular depression, which may be readily felt just above and behind the external auditory meatus and behind the auricle. This is the suprameatal triangle or MacEwan's triangle. The mastoid antrum usually communicates with the mastoid air cells; it is developed with the tympanum, and is therefore present at birth.

The anterior wall of the middle ear becomes somewhat narrowed down and funnel shaped. It consists of petrous bone, and opening into it are two canals. The upper transmits the tensor tympani muscle, the lower is that for the Eustachian tube. These two canals are separated from each other by a thin plate of bone called the processus cochleariformis. The Eustachian tube runs from the tympanum to the back of the naso-pharynx; the tympanic half of the tube is surrounded by bone, and the pharyngeal portion of the tube is surrounded by yellow elastic cartilage. The Eustachian tube is lined by a columnar ciliated epithelium, the cilia of which work towards the naso-pharynx and tend to prevent foreign particles from ascending the tube to the middle ear, especially when the nose is too forcibly "blown."

The Contents of the Middle Ear.—The middle ear contains three bones: the malleus, incus, and stapes. The handle of the malleus is attached to the umbo of the membrana tympani. The processus gracilis of the malleus runs forward down the Glasserian fissure. The head of the malleus articulates with the concavity of the body of the incus. Inserted into the neck of the malleus is the tendon of the tensor tympani muscle, which is innervated by the otic ganglion. The short process of the incus is attached by fibrous tissue, forming a ligament to the opposite wall of the tympanic cavity. The long process of the incus articulates with the head of the stapes. The foot of the stapes fits into the fenestra ovalis, and inserted into the neck of the stapes is the stapedius muscle. These three bones so articulate with one another, and are so placed, that the excursion of the stapes is found to be only about two-thirds of that of the handle of the malleus.

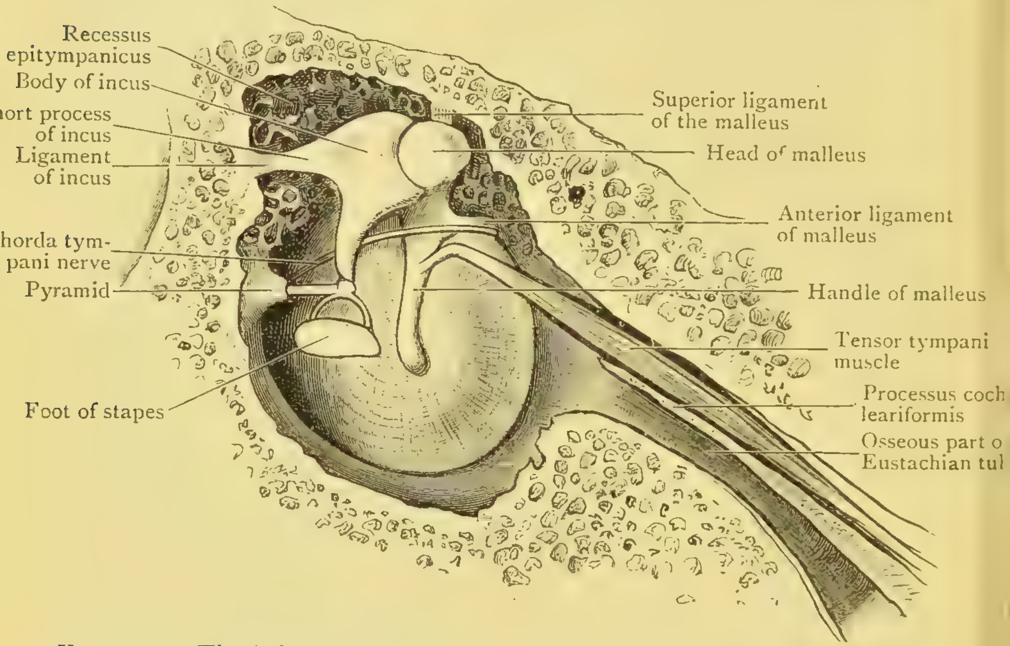


FIG. 124.—The left membrana tympani and the chain of ossicles seen from the inner aspect. (Howden, *from* Cunningham's Anatomy.)

In this way the amplitude of the vibrations, which are transmitted from the malleus through the incus to the stapes, is diminished about one-third. By means of the pull exercised by the tensor tympani muscle upon the neck of the malleus, the membrana tympani is kept tense. The action of the stapedius muscle is to slightly retract the head of the stapes, and so to render the bony lever less tense. There are true joints where these bones articulate with one another, and these are covered over by the mucous membrane reflected from the wall of the middle ear. The mucous membrane of the middle ear is covered by a columnar epithelium, many of the cells of which are ciliated and are continuous with the columnar ciliated cells which extend down the Eustachian tube.

The chorda tympani nerve comes off from the facial nerve just before it leaves the stylo-mastoid foramen; it enters the middle ear through the iter chordæ posterius, just below the pyramid. It crosses the posterior part of the membrana tympani lying between the handle of the malleus and the long process of the incus, leaving by the iter chordæ arterius, or canal of Huguier, to join the lingual nerve behind the ascending ramus of the lower jaw.

The Functions of the Middle Ear.—There is an advantage gained by having a solid element between the sound vibrations in the external atmosphere and the fluid (perilymph) in the internal ear; hence there is a solid rod present between the membrana tympani and the perilymph on the inner aspect of the fenestra ovalis. In the frog this is a cartilaginous rod called the columella. In the higher types this cartilaginous rod is replaced by three bones which articulate with one another, and are so arranged that they not only conduct the vibrations from the membrana tympani to the fenestra ovalis, but also modify the vibrations by diminishing their amplitude. At the same time, through this bony lever the membrana tympani may be put on the stretch by the action of the tensor tympani muscle, and the bony lever itself may be rendered less tense by the contraction of the stapedius muscle.

THE INTERNAL EAR.

The internal ear, or labyrinth, is situated deeply in the petrous portion of the temporal bone, and consists of two parts,—the osseous labyrinth and the membranous labyrinth. The osseous labyrinth includes the vestibule, three semicircular canals, each with an ampulla, and two and a half turns of the bony cochlea. These bony portions are all lined with endosteum, and contain the perilymph (liquor Cotunii). The membranous labyrinth which contains the endolymph is enclosed within the bony portion. The bony internal ear is connected with the middle ear by the fenestra ovalis and the fenestra rotunda; the foot of the stapes fits into the fenestra ovalis, which is the lower opening of the scala vestibuli, one of the canals of the bony cochlea; it contains perilymph.

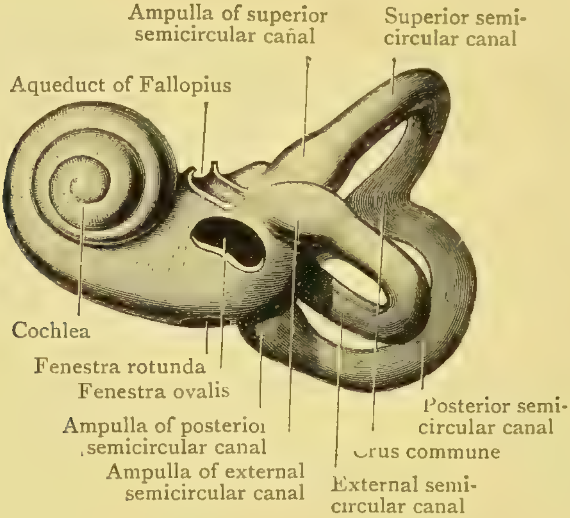

Ampulla of superior semicircular canal
Superior semicircular canal
Aqueduct of Fallopius
Cochlea
Fenestra rotunda
Fenestra ovalis
Ampulla of posterior semicircular canal
Ampulla of external semicircular canal
Posterior semicircular canal
Crus commune
External semicircular canal

FIG. 125.—Diagram of bony labyrinth (left), viewed from the outer side. (Cunningham, *after* Howden.)

The fenestra rotunda, which is filled in by the secondary tympanic membrane, is the opening to the scala tympani, one of the canals of the bony cochlea, which contains perilymph. The bony cochlea contains three canals, the scala vestibuli, the scala tympani, both of which contain perilymph, and the membranous canal, or the scala cochleæ, which contains endolymph. The scala vestibuli communicates with the scala tympani at the summit, or cupola, of the cochlea; the hole of communication is known as the helicotrema. The bony vestibule contains the membranous saccule, the saccus endolymphaticus, and the utricle. These contain endolymph, and are surrounded by perilymph. Contained within the bony semicircular canals are the membranous semicircular canals, which contain the endolymph, and are surrounded by perilymph (Fig. 126). The bony cochlea lies anterior to and somewhat below the vestibule and the semicircular canals. If a section is made through the bony cochlea it will be seen that it contains three compartments. The scala vestibuli with its perilymph is separated from the scala tympani with its perilymph, by the osseous spiral lamina which contains fibres of the auditory nerve. The scala cochleæ is separated from the scala vestibuli by Reissner's membrane, and from the scala tympani by the membranous spiral lamina which runs from the endosteum, lining the bony cochlea and the spiral ligament, to the free margin of the osseous spiral lamina. The scala cochleæ contains endolymph and the organ of Corti (*vide* Fig. 128). If it were possible to unravel and draw out straight the two and a half turns of the cochlea, the relationship of the bony and membranous canals to one another would appear somewhat as is shown in the next figure.

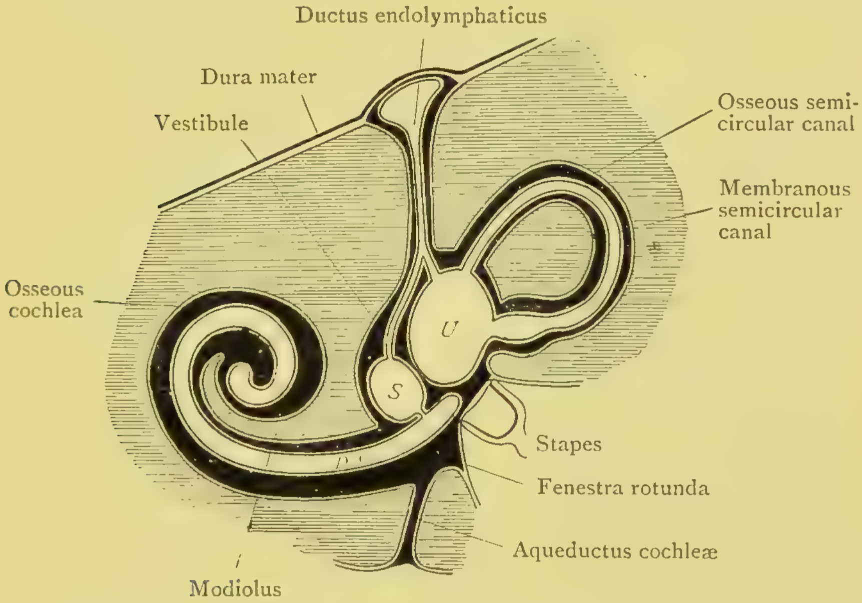


FIG. 126.—Diagram of the osseous and membranous labyrinth. (Cunningham, *modified from* Testut.)

S=Saccule.
U=Utricle.
D.C=Scala cochleæ.

The saccule communicates with the scala cochleæ by means of a short narrow tube, termed the canalis reuniens.

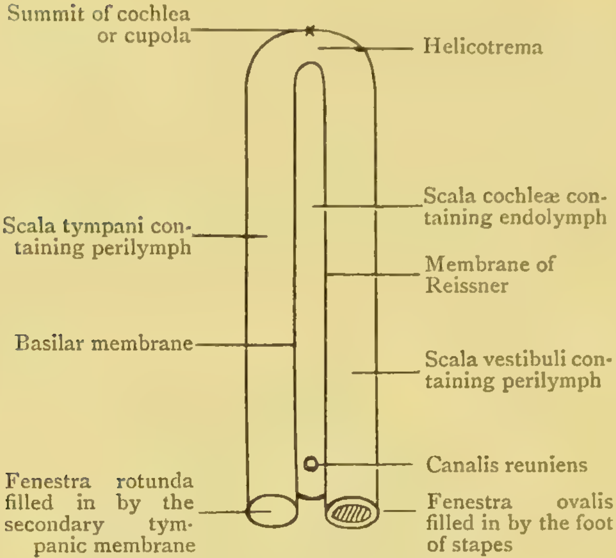

Summit of cochlea or cupola
Helicotrema
Scala cochleæ containing endolymph
Scala tympani containing perilymph
Membrane of Reissner
Basilar membrane
Scala vestibuli containing perilymph
Canalis reuniens
Fenestra rotunda filled in by the secondary tympanic membrane
Fenestra ovalis filled in by the foot of stapes

FIG. 127.

THE ORGAN OF CORTI.

The organ of Corti is situated in the scala cochleæ, and lies on the membranous spiral lamina or basilar membrane. This membrane runs from the limbus of connective tissue, which is found at the free margin of the osseous spiral lamina, to the spiral ligament by which the membranous spiral lamina is attached to the endosteum of the bony cochlea. The spiral ligament is somewhat strengthened by the accessory spiral ligament, which contains the blood vessel called the vas prominens. On the membranous spiral lamina are found the two sets of rods of Corti. It has been calculated that there are about 5600 inner rods of Corti and about 4000 outer rods. The outer rods are shaped something like a swan's beak, head, and neck. The inner rods are shaped something like the human ulna. The rods are finely fibrillated and inelastic, and their function is to support one another. They, on the other hand, are supported by cuboidal cells which lie on the membranous spiral lamina in the zona arcuata or tunnel of Corti. Attached to the upper portions of the rods of Corti are two membranes, the outer reticular lamina and the inner reticular lamina. These are shaped somewhat like a lattice work, and their function is to support the free portions of the hair cells. The hair cells are placed on either side of the rods of Corti. On section, two or three of these hair cells may be seen on the outer side of the outer rod, and one hair cell on the inner side of the inner rod. Each hair cell is a columnar ciliated epithelial cell with granular protoplasm, a central ovoid nucleus, and a tapering base, around which are arborisations from the fine nerve fibres which form the commencement of the auditory nerve. These nerve fibres pass from the bipolar nerve cells belonging to the spiral ganglion, contained in the osseous spiral lamina, along the membranous spiral lamina to the bases of the columnar hair-cells, where they arborise. The hair-cells are supported by columnar non-ciliated cells, known as the supporting cells of Deiters, and which become continuous with the cubical cells lining the endosteum of the scala cochleæ, and are reflected as flattened epithelial cells lying on the scala cochleæ surface of Reissner's membrane. They are reflected over the limbus, and line the spiral groove of the limbus, so becoming continuous with the supporting cells on the inner side of the inner hair-cells. Attached to

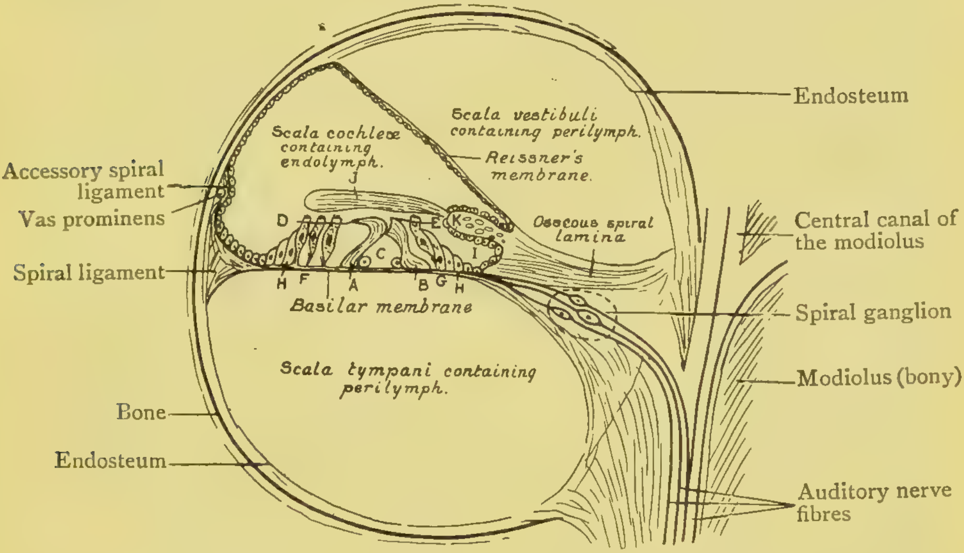


FIG. 128.—Diagram of a section through the bony cochlea showing the organ of Corti.

A. Outer rod of Corti (fibrillated).
B. Inner rod of Corti (fibrillated).
C. Tunnel of Corti.
D. Outer reticular membrane.
E. Inner reticular membrane.
F. Outer hair-cells with nerve arborisations.
G. Inner hair-cells with nerve arborisations.
H. Supporting cells of Deiters.
I. Spiral groove.
J. Membrana tectoria.
K. Limbus.

the free margin of the limbus is an extremely fine fibrillated membrane floating in the endolymph, which is known as the tectorial membrane lying immediately over, and is probably in contact with the hairs of the hair-cells. It should be noted that the membranous spiral lamina increases in size from below upwards, so that its widest part is at the helicotrema, and here the rods of Corti are set more obliquely, and the tunnel so formed is lower.

Functions of the Internal Ear.—The vibrations which have been transmitted to the foot of the stapes cause a movement of the perilymph in the scala vestibuli. This movement is transmitted up the two and a half turns of the cochlea over the helicotrema to the perilymph contained in the scala tympani, and in this way vibrations are readily transmitted to the membranous spiral lamina. Any movement of the foot of the stapes inwards towards the scala vestibuli is compensated by a bulge of the secondary tympanic membrane at the fenestra rotunda outward towards the middle ear. This movement is transmitted through the perilymph in the scala vestibuli and tympani. The vibrations so set up in the perilymph are transmitted to the specialised nerve epithelial cells called the hair-cells. Their function is to receive the stimuli, and to convert them into definite afferent nerve impulses, which are conducted along the fine fibres of the auditory nerve through the spiral ganglion into the main auditory nerve contained in the modiolus, and so back to the hind brain. It has been suggested that the vibrations in the scala vestibuli are transmitted through Reissner's membrane to the endolymph, and by it through the tectorial membrane, and so to the hairs of the hair-cells. But it is rather more likely, however, that the tectorial membrane acts, not as a transmitter, but as a damping agent representing somewhat the check action as shown in a piano.

The auditory sense is very highly developed. Tones varying in pitch from 20 to 60,000 vibrations per second may be detected. Exner states that sounds can be recognised as distinct if the interval between them is not less than 0·002 second.

THEORIES OF HEARING.

It is not yet determined how the organ of Corti acts, but the membranous spiral lamina, or basilar membrane, is most probably that portion of the organ which receives the vibrations from the perilymph, and the hair cells are directly influenced through the basilar membrane.

The Telephone Theory of Rutherford and Waller.—The basilar membrane vibrates *as a whole*, and responds in a different way to different tones or combinations of tones, just as the membrana tympani does, and so gives rise to different patterns of vibrations which are communicated to the hair-cells. The hair-cells originate the afferent nerve impulses; these travel to the auditory centre in the brain, where discrimination between different sounds takes place.

The Resonance Theory, or Piano Theory, of Helmholtz.—The fibres which make up the basilar membrane differ in length, the shortest fibres being below; the length of the fibres increases up to the helicotrema. Each fibre vibrates in unison with the tone to which it is attuned, and so each tone affects definite hair-cells, which are supported by the particular fibre which vibrates. The sound is, according to this theory, analysed in the internal ear. The high notes are detected in that part of the cochlea in which the short fibres are, and the low notes detected in that part of the cochlea in which the long fibres are. One weak point in this theory is that one fibre *cannot* vibrate alone and independently of its neighbours.

Gray's Modification of Helmholtz's View gets over the chief objection to the theory. His modification is based upon the *principle of maximum stimulation.* He refers to the fact that, if pressure is made upon the skin of the finger with a moderately sharp-pointed object, a sensation of pressure is felt at that point; if the pressure is increased, although it involves a considerable area, one is still conscious of the pressure only at one point, although a comparatively large number of nerve endings is involved. One is conscious only of the stimulation of that nerve-ending or endings at the point of maximum stimulation. If, therefore, instead of limiting the movement of the basilar membrane to a particular fibre, when the corresponding note is sounded, the whole or a large part of the membrane is set in vibration, the fibre that is in exact sympathy with the note sounded would vibrate to a maximum extent, and the individual would consequently be conscious of that note only (Macleod Yearsley).

Myers has advanced the view that the hair-cells themselves may be specially attuned to respond to one of the many tonal stimuli which reach them.

THE CONNECTIONS OF THE AUDITORY NERVE.

The nerve fibres from the spiral ganglion form the cochlear division of the (eighth) auditory nerve. Some of these fibres

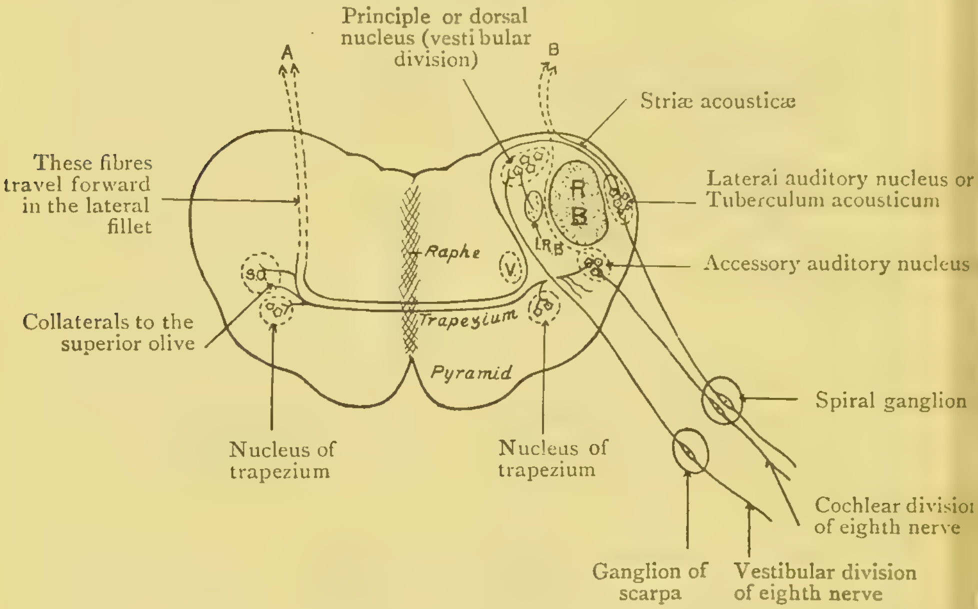

Principle or dorsal nucleus (vestibular division)
A
B
Striæ acousticæ
These fibres travel forward in the lateral fillet
Lateral auditory nucleus or Tuberculum acousticum
R B
I.R.B.
Raphe
V.
Accessory auditory nucleus
S.O.
Collaterals to the superior olive
Trapezium
Pyramid
Spiral ganglion
Nucleus of trapezium
Nucleus of trapezium
Cochlear divisio of eighth nerve
Ganglion of scarpa
Vestibular division of eighth nerve

FIG. 129.—Diagram of the connections of the eighth cranial nerve in the medulla and pons Varolii.

A. = Fibres to the mesial corpus geniculatum and the posterior corpus quadrigeminum.
B. = A few fibres from the accessory auditory nucleus and the lateral auditory nucleus to the mesial corpus geniculatum and the posterior corpus quadrigeminum of the same side.
R.B. = Restiform body.
I.R.B. = Internal restiform body.
V. = Descending root of the fifth nerve.
S.O. = Superior olive.

enter the hind brain external to the restiform body and make cell stations in the lateral auditory nucleus, or tuberculum acousticum (ganglion of the root). New fibres arise in this nucleus, which travel over the restiform body and form the striæ acousticæ in the floor of the fourth ventricle. These fibres dip down internal to the restiform body to gain the trapezium (*vide* Fig. 129). Other fibres enter the hind brain ventral to the restiform body and make cell stations in the accessory auditory nucleus, which lies ventral to the restiform body. From this nucleus new fibres arise which give off collaterals to the superior olive and the nucleus of the trapezium of the same side and then become the fibres of the trapezium, crossing the median raphé to gain the opposite side of the pons Varolii. On reaching the opposite side these fibres give off collaterals to the superior olive and to the nucleus of the trapezium. They then travel forwards in the lateral fillet—traversing the tegmentum of the mid-brain, and eventually make cell stations in the mesial corpus geniculatum and in the posterior corpus quadrigeminum.

From the cell station in the mesial corpus geniculatum new fibres arise, which traverse the auditory radiation in the hindmost part of the internal capsule of the corpus striatum, and after travelling through the corona radiata ultimately reach the temporo-sphenoidal lobe of the brain. It will be seen then that for the most part the right organ of Corti, through the spiral ganglion, is connected with the left temporo-sphenoidal lobe of the brain.

From some of the nerve cells in the tuberculum acousticum and in the accessory auditory nucleus fibres arise which appear to pass forwards on the *same* side through the pons. They make cell stations in the mesial corpus geniculatum and in the posterior corpus quadrigeminum. From the cell station in the mesial corpus geniculatum new fibres arise which traverse the hindmost part of the internal capsule (auditory radiation), and they ultimately reach the temporo-sphenoidal lobe of the brain upon the *same* side. It will be seen then that the organ of Corti is not only connected with the temporo-sphenoidal lobe of the *opposite* side of the brain, but also with the temporo-sphenoidal lobe of the *same* side. The auditory centre is located in the superior temporo-sphenoidal lobe on its convex aspect, but the centre also extends into the anterior transverse temporal convolution of Heschl (or Flechsig's auditory gyrus), which is situated on the upper or Sylvian surface of the temporal lobe at the bottom of the Sylvian fossa, close behind the island of Reil. Heschl's gyrus is directly continuous with the superior temporal gyrus. Each cortical centre receives auditory impulses from both organs of Corti, although more extensively from the organ of Corti of the contra-lateral side. A lesion in one temporo-sphenoidal lobe does not result in deafness. In right-handed people there is a specially differentiated portion of the *left* auditory centre, which is an association centre for word-sounds.

Summing up, then, the functions of the various parts of the ear, the pinna, or auricle, picks up sound waves in the atmosphere and transmits them through the external auditory meatus, down the external auditory canal. These vibrations impinge upon the membrana tympani, which is set vibrating. The vibrations from the membrana tympani are conducted across the malleus, incus, and stapes, where the amplitude of vibration is somewhat diminished, though the force of vibration is slightly increased. The vibrations so modified are transmitted through the foot of the stapes to the fenestra ovalis, thence up the perilymph in the 2½ turns of the scala vestibuli, over the helicotrema, down the perilymph of the scala tympani, from the scala tympani to the membranous spiral lamina, whence the specific stimulus, the vibrations are received by the hair cells, and converted by them into *afferent nerve impulses,* which travel back along the fine fibres of the auditory nerve contained in the canals in the osseous spiral lamina. The nerve impulses pass through the bipolar nerve cells contained in the spiral ganglion, and thence through the cochlear division of the auditory nerve to the hind brain. Through the auditory cell stations in the pons some of the impulses pass up through the pons, through the tegmentum of the crus cerebri, and through the internal capsule of the corpus striatum to the auditory centre in the temporo-sphenoidal lobe on the *same* side of the brain. Most of the nerve impulses, however, *cross* in the trapezium of the pons to the opposite side, and travel up through the pons, then through the tegmentum of the crus cerebri in the lateral fillet, and through the internal capsule of the corpus striatum; thence by the corona radiata to the superior temporo-sphenoidal lobe of the brain. That is to say, auditory impulses from the right ear go chiefly to the left cerebral cortex, but some of the impulses arrive at the cerebral cortex of the same side.

The anterior three-fourths of the superior temporo-sphenoidal lobe of the brain constitute the auditory receptive centre, called the audito-sensory centre. Just behind this is a more highly developed centre, the probable function of which is to recognise the import of sounds, especially of spoken words; it is known as the audito-psychic centre. If a lesion of this centre occurs, word deafness follows. The audito-psychic centre is the higher association centre for hearing, and works in harmony with the other association centres of the brain.

Bilateral Hearing.—By means of the use of two ears the position of the source of a sound in space is determined. Sound waves originating on the right will, in normal circumstances, affect the right ear more than the left, a comparison of the intensity of the two sets of auditory sensations produced is made, and a judgment arrived at with regard to the direction of the origin of the sound in space.

CHAPTER LIII.

THE ORGANS OF THE VESTIBULE.

THE organs of the vestibule are contained in the three semicircular canals, the utricle, and the saccule. If a section is made through one of the bony semicircular canals it will be seen that the bony canal is lined on its inner aspect by a fibrous endosteum; this endosteum helps to form a separate membranous semicircular canal which contains endolymph. Between the membranous semicircular canal and the bony semicircular canal is the perilymph. There are fine fibrous strands, which run from the membranous semicircular canal

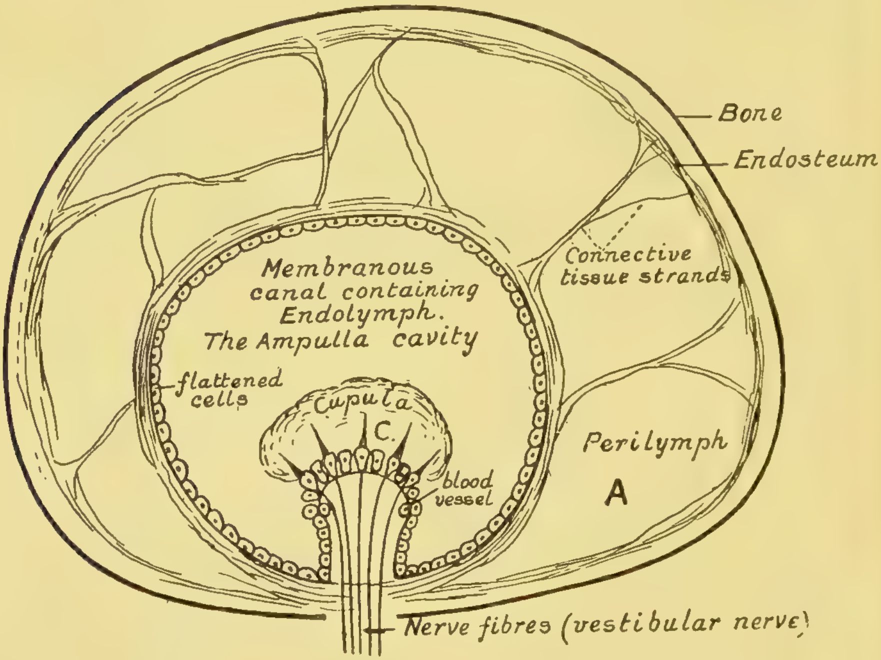

Bone
Endosteum
Connective tissue strands
Membranous canal containing Endolymph. The Ampulla cavity
flattened cells
Cupula
C.
blood vessel
Perilymph
A
Nerve fibres (vestibular nerve)

FIG. 130.—Diagram of a section through an ampulla of a semicircular canal showing the crista C.

A. = The bony semicircular canal containing perilymph.

to the endosteum lining the bony semicircular canal in order that the membranous semicircular canal may be held in position. Within the three ampullæ of the membranous semicircular canals are specialised structures which contain sensory nerve-epithelial cells; these structures are called the *cristæ.* There are similar structures found in the utricle and in the saccule; these are the *maculæ.* The histological structure of one of the *cristæ* is as follows (*vide* Fig. 130):—

Each membranous semicircular canal is lined by a flattened epithelium, but in the region of the ampullæ, where the membranous canal is intimately attached to the bony canal, the epithelium becomes specialised and takes part in the formation of the crista.

A small hillock is formed by the sub-epithelial tissue, which is traversed by non-medullated nerve fibres of the vestibular division of the auditory nerve. At the top of the hillock these fibres pierce the basement membrane which supports the specialised cells. On the fine basement membrane there are two kinds of modified columnar cells, which are continuous with the flattened cells lining the membranous canal; these cells are the specialised nerve-epithelial cells (hair-cells) and the supporting cells of Retzius (*vide* Fig. 131).

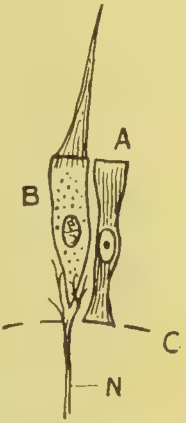


FIG. 131.—Diagram of two cells from a crista.

A. = A fibre cell of Retzius supported upon the basement membrane C.
B. = Hair-cell with a long tapering hair which projects into the cupula.
N. = Non-medullated nerve fibre arborising around the base of the hair-cell.

The Specialised Nerve-Epithelial Cell.

Each cell is columnar in shape; there is a central oval nucleus, and the protoplasm is full of fine granules. The basal portion of the cell tapers somewhat, and around this portion there is an arborisation of fine non-medullated nerve fibres. The protoplasm of the distal portion of the cell is continued into a rather coarse and hair-like process. These processes from the nerve-epithelial cells or hair-cells project into a cap of mucous-like material known as the cupula. Between the nerve-epithelial cells are the supporting cells of

Retzius. These are columnar in shape, the base is broad and is supported on the basement membrane. The nucleus is central and oval and the protoplasm fibrillated. The supporting cells are not ciliated, and are not connected with nerve endings. The structure of the macula of the saccule and of the utricle is somewhat similar to that of the cristæ, except that the cupula of the saccule and utricle contains small particles of $CaCO_3$, called otoliths.

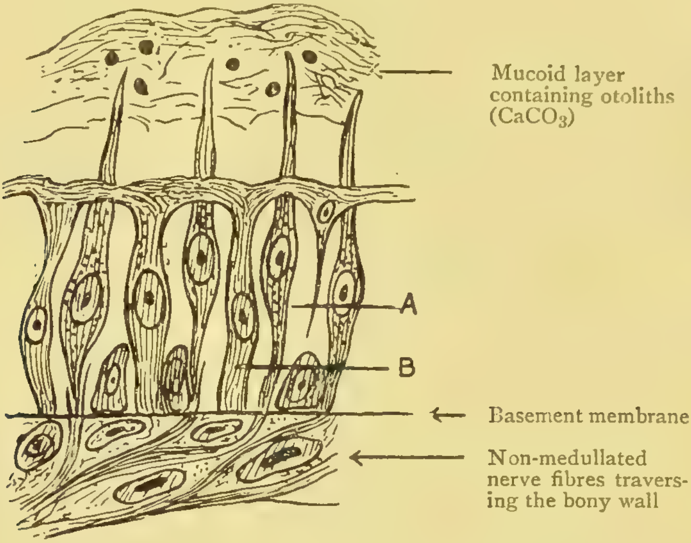

Mucoid layer containing otoliths ($CaCO_3$)
A
B
Basement membrane
Non-medullated nerve fibres traversing the bony wall

FIG. 132.—Section through the central portion of the macula of the saccule of a cat (diagrammatic). (Modified from a drawing lent by Professor Urban Pritchard.)

A. = Hair-cell (specialised nerve-epithelial cell).
B. = Supporting cell of Retzius.

THE NERVE CONNECTIONS OF THE VESTIBULAR PORTION OF THE MEMBRANOUS LABYRINTH.

The vestibular division of the eighth nerve commences in arborisations around the nerve-epithelial cells of the three cristæ contained in the membranous ampullæ, and around those of the maculæ contained in the utricle and saccule. These nerve fibres at once converge to the cells contained in the vestibular ganglion (ganglion of Scarpa). This ganglion is placed immediately outside the utricle, the cells contained in it are bipolar, and therefore similar to those present in the spiral ganglion contained in the osseous spiral lamina. The proximal processes of these cells form the vestibular division of the eighth nerve, which enters the hind brain below the restiform body, passing in between the restiform body and the descending root of the fifth nerve (*vide* Fig. 129). The fibres course dorsalwards to the principal or dorsal nucleus of the vestibular division of the eighth nerve, which constitutes the cell station for these fibres. From the cells in the vestibular nucleus new fibres arise, which divide into ascending and descending branches. The descending branches form a small descending vestibular root which runs back to the lower part of the medulla oblongata, where the fibres arborise around cells which constitute the descending vestibular nucleus. The ascending branches pass up in the internal restiform body and the inferior cerebellar peduncle to the homolateral part of the cerebellum. The ascending branches give off collaterals which arborise around nerve cells in the nucleus of Deiters and the nucleus of Bechterew, both of which are in the immediate vicinity of the restiform body. According

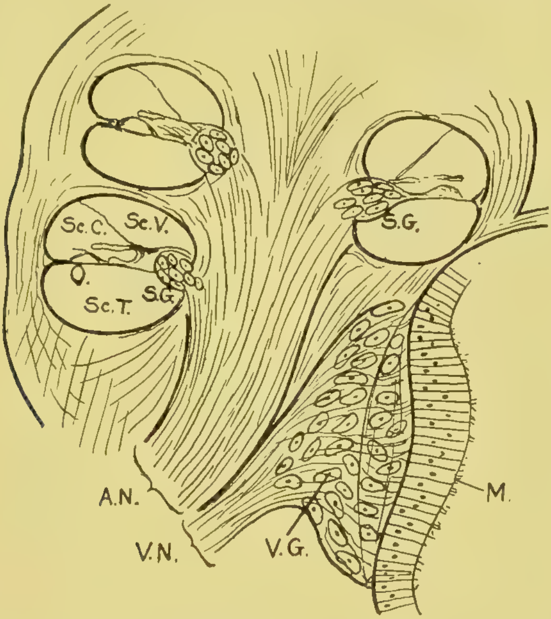


FIG. 133.—Section through the internal ear of a cat, showing the spiral and vestibular ganglia. (From a preparation lent by Professor Urban Pritchard.)

A.N. = Fibres of auditory nerve.
V.N. = Fibres of vestibular division of the eighth nerve.
S.G. = Spiral ganglion.
V.G. = Vestibular ganglion (of Scarpa).
Sc.V. = Scala vestibuli.
Sc.T. = Scala tympani.
Sc.C. = Scala cochleæ.
.O. = Organ of Corti.
M. = Macula.

to some authorities, however, collaterals from the ascending branches go to the nucleus of Bechterew, and those from the descending branches go to the nucleus of Deiters. There is no evidence of any crossing in the brain of the vestibular fibres of the eighth nerve.

LABYRINTHINE IMPRESSIONS.

Alterations of pressure of the endolymph, bathing the cristæ and the maculæ, act as the specific stimuli, which cause the specialised nerve-epithelium of these organs to transmit these labyrinthine impressions along the vestibular division of the eighth nerve to the cerebellum, which aid the cerebellum in performing its function of controlling the equilibrium of the body. In certain circumstances, abnormal impressions may arise in the labyrinth, as the following examples indicate. If an individual is placed on a revolving stool, and the stool is rapidly rotated and then suddenly brought to a standstill, the individual experiences the sensation as if he is being rotated in the opposite direction. He may experience a sensation of giddiness, lose his equilibrium, and fall over.

Amongst other causes, Menière's symptoms *may* be set up by a vasomotor disturbance, or be due to a hæmorrhage in the membranous labyrinth. These abnormal conditions in the internal ear, besides producing tinnitus aureum (buzzing in the ear) and deafness, may result in abnormal impressions travelling by the vestibular nerve to the cerebellum, the result of which is somewhat similar to that which may be experimentally produced as just described, namely, sensations of giddiness, loss of equilibrium, and sometimes a fall.

SECTION XIV.

ELEMENTARY MENTAL PHYSIOLOGY.

CHAPTER LIV.

It has already been pointed out that the central cells lining the acini of the salivary glands contain fine zymogen granules, which are after a time extruded from the cells, and eventually become part of the saliva. In other words, the cells lining the acini of the salivary glands *secrete* saliva. The nerve cells present in the grey matter of the brain, when treated by Nissl's methylene-blue method of staining, appear to contain spindle-shaped granules. It may be that these granules are produced artificially by the histological treatment to which the cells have been subjected. If this is so, the material of which these granules are formed must exist in some condition or other during the living condition of the cell, although that condition may not be in the shape of spindle-shaped granules. The kinetoplasm of which these granules are composed is certainly used up when the cells actively function. There is no evidence, however, that the nerve cells of the brain secrete mental processes in the same way that the cells of the salivary glands secrete saliva. It is not right to assume, therefore, that mental activity is the outcome of the physiological activity of the nerve cells of the cerebral cortex, though there would be no mental activity if the cells of the cerebral cortex did not perform their function in an appropriate manner.

It is usual to assume that the two activities, physiological and mental, of the cortical cells of the brain run parallel with one another. This is the principle of psycho-physical or mento-physiological parallelism, which indicates that the bodily processes are the condition of the mental processes. Mind consists of a *stream of mental processes* which are ever changing, like a stream which is constantly flowing. "Mind now" constitutes consciousness, *i.e.* consciousness is "mind now." Just as mental processes are ever changing, so must *consciousness* be ever changing too. From this it will be understood that consciousness is not a "state," but consists of a stream of mental processes which are ever flowing onward. There are three conditions of consciousness—

1. The waking consciousness, in which, however, there are two distinct states, the *attentive state* and the *inattentive state.*
2. The dreaming consciousness.
3. The hypnotic consciousness.

ANALYSIS OF MIND.

Mind may be defined as the sum of all those mental processes which make up the experience of a single lifetime. "Mind now" is present consciousness, and consciousness is made up of a number of concrete mental processes, such as percepts, ideas, feelings, etc.

Each concrete mental process consists of a number of mental elements, and mental elements consist of sensations and affections which are always experienced together.

There are therefore two classes of elementary mental processes, *sensations* and *affections.* A number of *sensations* arising in consciousness together form a percept, which is a concrete mental process. An orange may be taken as an example. If it is placed in view upon a table it may be perceived, *i.e.* the percept of an orange arises in consciousness. If the percept is analysed it will be found to consist of sensations of form, of size, of colour, of smell, of touch, of weight, etc.—in other words, a number of sensations occur in consciousness; together these produce a concrete mental process, that is, a percept.

These sensations may be centrally aroused without an external object providing the necessary stimuli; an orange may be ideated. An individual may form a definite idea of an orange. Every idea, however, seems to be overlaid by the *Ego*, the personal equation of the individual. It will be understood, therefore, how it is that different individuals construct and maintain different ideas; each individual's ideas are moulded by his Ego.

The "Brown-idea" consequently differs from the "Smith-idea," for it is the *Ego* which experiences the conscious processes, the Ego which moulds the ideas, the Ego which senses and feels. Ideas become associated together in consciousness according to the formula, $a\underparen{b,b}\overparen{c,c}\underparen{d,d}e$, and in this way a train of ideas arises, the connecting link being a sensation common to any two ideas. The physiological condition of the association of ideas is *habit.*

Habit is the tendency of a thing to be, or to do now what it was, or did, on some previous occasion, and the law of habit runs through nature (Titchener).

Memory may be defined as a *marked idea*, and there are four idea or memory types—

1. The visual type.
2. The auditory type.
3. The kinæsthetic type.
4. The mixed type.

Some students, for instance, remember their physiology by reading a text-book, looking at diagrams, and by seeing experiments performed, others more readily remember what they hear at lectures, others again well remember the experiments which they have personally performed ; but, as a rule, the student of the *mixed memory type* acquires most useful knowledge, for he learns by reading the text-book, by seeing experiments, by listening to the lectures, and by performing his own experiments in the laboratory.

Whenever sensations arise in consciousness, affection occurs too, for an *affection* is an elementary conscious process which may be set up by the stimulation of any bodily organs. As a rule it is the new sensations which are distinctly affective, but, with repetition of the sensations, the affection begins to wear off. Whenever one sees the new pretty picture hanging upon the wall of one's room the perception (concrete sensation) is pleasing (we are affected), but after a time the "newness" wears off, one gets "in the habit" of seeing the picture in its position, consequently the affection becomes gradually less.

There are two kinds of affection, *pleasant* and *unpleasant*, but with most "everyday" sensations the "pleasantness" and the "unpleasantness" wear off ; this, however, is not the case with organic sensations. As a rule all organic sensations, *i.e.* those derived from the internal organs, are definitely affective.

Sensations, perceptions, and ideas which are over-ridden by affection—that is, those which are very clearly affective—are termed *feelings.* When there is present in consciousness a complex process made up of sensations, and *pleasantness*, or *unpleasantness*, and when the affective side of the process, that is, its pleasantness or unpleasantness, strikes one more forcibly than the sense side, the total process is called a *feeling* (Titchener).

Feelings (*i.e.* organic sensations over-ridden with affection) derived from the stomach after a good meal are pleasant, and give rise to the conscious process of *bien être.* Generally speaking, people *feel* more generous *after* they have become "satisfied" by a good dinner than before such an event. On the other hand, feelings derived from the organic sensations of pain, which arise when the intestine becomes over-distended, and is contracting irregularly (intestinal colic), are particularly affective and distinctly unpleasant.

Whenever feelings (*i.e.* sensations over-ridden by affection) arise in consciousness, *attention* appears in consciousness also. It may be said, therefore, that with affection comes attention, for affection and attention are considered as the obverse and reverse of the same conscious process. Organic sensations, which enter into one's feelings with especial readiness, are particularly apt to attract one's attention. Inherited tendency indicates that one *must attend to* pleasant and unpleasant feelings, but acquired tendency indicates that one must of necessity *attend to* other matters, such as one's professional work or daily occupation.

SENSATIONS.

It has been stated already that sensations are the elementary mental processes. These sensations on the physiological side depend upon—

1. A nerve end-organ situated in a receptive epithelium, which is adapted to receive a specific stimulus.

2. An afferent nerve-path, capable of transmitting the nervous impulse from the end-organ to the brain.

3. A receptive centre in the cerebral cortex, capable of receiving the afferent nerve impulse.

4. Other association centres, which work in harmony with the chief receptive centre.

Every peripheral receptive end-organ is so constituted that it responds to a particular form of stimulus, *e.g.* the retina responds to light waves, and the organ of Corti to sound waves. The stimulus, to which the receptive end-organ is thus adapted to respond, is called the *adequate* or *homologous* stimulus. On the other hand, a receptive end-organ will often respond to an *inadequate* stimulus; thus a blow on the eyeball often produces sensations of bright light, a blow on the ear produces sensations of sound, electrical stimulation of the mucous membrane of the tongue gives rise to sensations of taste. Between the application of the stimulus and the resulting sensation there is an appreciable lapse of time, which is called the latent period. The delay is produced chiefly in the synapses which are present in the central nervous system; in other words, it takes longer for a nervous impulse to traverse four small neurones than two long neurones. The latent period for a light sensation is longer than for a sound sensation, and longer for a painful sensation than for a pressure sensation.

A sensation always lasts longer than the stimulus which produced it: the sting lasts longer than the blow. This fact accounts for the positive after-images which follow strong stimulation of the retina. In disease of nerve cells and nerve fibres which results in nerve degeneration, the nervous impulses which give rise to sensations may be definitely delayed in their transit, or may never be transmitted at all. In locomotor ataxia there is a definite retardation of those nervous impulses which give rise to pain, and in this disease there is often a loss of power of localising the origin of stimuli, which produce sensations of pain; for instance, if a patient is pricked over the right patella he may say he feels the pain over the *left* patella. This phenomenon is called *allocheiria*, and it may be due to the fact, which Head first pointed out, that the mind projects sensations, which arise in an area of lowered sensibility, to the area of higher sensibility, which is related most closely to it by nerve connections within the brain and spinal cord.

Generally speaking, it may be said that sensations differ from each other in *modality*, in *quality*, in *intensity*, in *extensity*, and in *local signature.*

Modality.—This indicates that different sensations are derived from different receptive end-organs, *e.g.* sensations of light are derived from the retina, sensations of sound from the organ of Corti, sensations of taste from the tongue, etc.

Quality.—Sensations derived from the same organs differ from one another in quality. Sensations of red and green arise from the retina, but they differ from one another in quality.

Intensity.—A stimulus must be of a certain strength in order that a sensation is produced; too slight a pressure produces no sensation. That strength of stimulus, which is *just* enough to produce a sensation, is called the liminal value of the stimulus, or its absolute threshold. Sensations differ from one another in strength or intensity. The sensation of pressure may be produced by the pressure of an ounce, or of a pound; the quality is the same (*i.e.* pressure), the intensities are different.

WEBER'S LAW.—There is a definite relationship between the strength of the stimulus and the intensity of the sensation which it produces. Weber found, in experimenting with weights, that it was just as difficult to distinguish between the pressure of 29 and 30 half-ounces as between the pressure of 29 and 30 drachms; although the difference of weight in the former case is four times as great as it is in the latter (8 drms. = 1 oz.). Sameness of difference in sensation means proportional sameness of difference between stimuli (Titchener).

Fechner went further, and suggested that there was a mathematical exactness between the strength of the stimulus and the intensity of the sensation.

Stimulus	of strength	1	produces intensity	of sensation	P.
,,	,,	2	,,	,,	2 P.
,,	,,	4	,,	,,	3 P.
,,	,,	8	,,	,,	4 P.
,,	,,	16	,,	,,	5 P.

In other words, the strength of the stimulus must increase in geometrical progression in order that the intensity of the sensation may increase in arithmetical progression, or sensations increase directly as the logarithm of the stimuli which produce them. The difference in strength of the two stimuli must not fall below a certain definite minimum, otherwise no difference of intensity of sensation can be appreciated. There is a liminal value for a stimulus difference, which is known as the differential threshold of the stimulus. Generally speaking, therefore, with an increase of stimulus there is an increase of sensation, but after a time a maximum limit is reached whereby no further increase of the strength of the stimulus produces any increase in intensity of the sensation.

The value of the differential threshold of different stimuli has been worked out. In the case of light it is about $\frac{1}{100}$. If the sensation of light obtained from 100 lighted candles is Q, the sensation of light which arises from 101 lighted candles is Q +, *i.e.* the least increase of intensity of sensation. If the sensation was produced by the stimulus of 1000 lighted candles, 10 would have to be added in order that the intensity of the sensation might be increased.

Extensity.—By extensity is meant "the spreadoutness" of a sensation. This attribute of sensation is most highly developed in those sensations derived from the skin and from the retina. Sensations of smell and taste appear to be almost devoid of extensity.

Local Signature.—"Every point stimulated on the retina or skin has its local signature or sign, in virtue of which one is able to localise the stimulus at that point, and to distinguish the sensation from that produced by the stimulation of a neighbouring point. On the basis of extensity and local signature is built up the perception of extension, form, and spatial relations generally" (C. S. Myers).

An *illusion* is a false perception of an external impulse. In this way sensations are judged to be different from what they really are. The railway lines, when looked at for a distance, *appear* to converge, although in reality this is not the case. This is an example of an optical illusion. In other words, one does not always perceive aright. The cause of illusions is partly in the peripheral receptive organs, and partly also due to central (brain) factors. The sensory or receptive end-organs are not always equal to the demands required of them, and one's nervous tendencies may lead one "to see what is not there, or to fail to see what is."

From the skin there arise impulses which result in sensations of pressure, heat, cold, and pain; from muscles, muscle sense, and from the tendons, tendon sense. From the skin, muscles, tendons, ligaments, and synovial membrane kinæsthetic sensations arise. From the upper part of the mucous membrane of the nose sensations of smell arise. From the taste-buds of the tongue and palate sensations of taste arise. Sensations of thirst arise in the posterior pharyngeal wall; sensations of heat, cold, and pain from the œsophagus; feelings of hunger, satiety, and *bien être* from the mucous membrane of the stomach. Feelings which are definitely affective originate from the other viscera; cf. the discomfort of a full rectum, the discomfort and even painful sensations of a distended bladder, and the sensations of excruciating pain which are experienced during the passage of gall-stones along the bile ducts, or the passage of a renal calculus along the ureter. Painful sensations are experienced when nervous impulses arise in the abdomen and pelvis, which are caused by injury to, or inflammation of, the parietal layer of peritoneum.

From the retina impulses arise which result in sensations of form, size, and depth in space, also in sensations of colour. From the organ of Corti impulses arise which result in sensations of noise and tone.

Under experimental conditions upon the labyrinth of the internal ear, and in disease of that region, abnormal nervous impulses reach the brain which result in the sensations of giddiness.

SECTION XV.

REPRODUCTION.

CHAPTER LV.

THE continuity of the species, both of plants and of animals, is dependent upon their reproduction. The physiology of reproduction embraces a wide field, but the subject will be dealt with here only from the standpoint of human physiology, without entrenching upon the special domain of Embryology.

Reproduction is inaugurated in the human subject by the union of two different sexual elements, the spermatozoon of the male and the ovum of the female. This act of union is known as *conjugation.*

The spermatozoon is formed in the testis, the ovum in the ovary. The spermatozoa are introduced into the female by the act of copulation. If the spermatozoon and ovum meet they conjugate, or unite, and the ovum is said to become fertilised. As a result of this conjugation the oösperm, or fertilised ovum, is produced. This develops within the body of the female to form a new individual, the fœtus. When the fœtus has reached a certain stage of development it is expelled from the body of the mother by the act of parturition: this constitutes its birth.

The newly born individual is not at once sufficiently developed to make use of the ordinary food of its species, and is for a considerable time dependent upon its mother for nourishment. For this purpose the mammary glands of the mother acquire a high grade of activity in producing the milk, which provides for the maintenance of the new-born child, and for which it is a perfect food both in quantity and in composition.

In discussing the physiology of reproduction the following subjects will be dealt with :—

1. The functions of the male and female reproductive organs.
2. Copulation and fertilisation.
3. Parturition.

THE MALE REPRODUCTIVE ORGANS.

The essential male reproductive organs are—

1. The testes, which produce the spermatozoa.
2. The accessory sexual glands, *e.g.*, the vesiculæ seminales, the prostate gland, and the glands of Cowper, which produce secretions which mix with the spermatozoa and help to constitute the seminal fluid.
3. The penis, the organ of copulation by means of which the seminal fluid is introduced into the vagina of the female.

1. **The Testes.**—These are ovoid bodies, suspended by means of the spermatic cord in the scrotum. They produce the spermatozoa and an internal secretion (*vide* p. 292).

Each testis is enclosed in the tunica albuginea. This is a strong thick capsule consisting of white fibrous tissue, and a small amount of unstriped muscle. The tunica albuginea is covered externally by the visceral layer of the tunica vaginalis, the serous coat which invests the testis, and the epididymis.

The tunica albuginea is prolonged as an incomplete vertical septum into the posterior aspect of the testis to form the mediastinum testis, or corpus Highmorianum ; septa pass from the tunica albuginea towards the mediastinum testis, subdividing the organ into a number of compartments, with their bases directed outwards, and their apices towards the mediastinum testis. Each compartment contains several tubuli seminiferi, or seminal tubules, which are long convoluted tubules, and which rarely branch except in the cortical zone of the testis at their outer ends. The tubules are directed towards the mediastinum testis, where they unite with a few straight tubules, the tubuli recti. The tubules then open into a dense network of irregular tubules in the mediastinum to form the rete testis (*vide* Fig. 134).

From this network there proceed some twelve to fifteen ducts, the vasa efferentia, which emerge from the testis and form a series of conical eminences, the coni vasculosi, which constitute the head of the epididymis. These tubules gradually unite, and then form the globus major and the globus minor of the epididymis. They eventually terminate in the vas deferens, or the excretory duct of the testis. The vas deferens is a thick-walled tube, on the outside of which there is a layer of plain muscle, the fibres being longitudinally arranged. Within this is a thick circular coat of plain muscle, and internal to this a thin layer of longitudinally arranged plain muscle. The mucous membrane of the tube is lined by columnar non-ciliated epithelial cells. Supporting the tubuli seminiferi of the testis is a stroma of fine sustentacular fibres, containing, in addition to blood vessels and lymphatics, a number of large polyhedral interstitial cells with large nuclei. These cells are of a yellow colour, and sometimes contain crystalloid bodies. These interstitial cells in all probability produce the internal secretion of the testis.

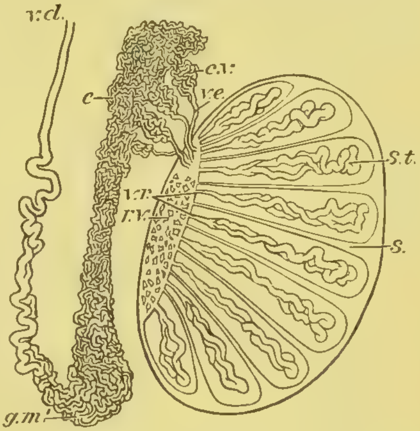


FIG. 134.—Diagram to illustrate the structure of the testicle. (*From* Cunningham, *after* A. F. Dixon.)

s. = Septula testis.
s.t. = Seminiferous tubule.
v.r. = Tubuli recti.
r.v. = Rete testis in the mediastinum testis.
v.e. = Vasa efferentia.
c.v. = Coni vasculosi.
c. = Globus major.
g.m.' = Globus minor.
v.d. = Vas deferens.

COMPOSITION OF SEMINAL FLUID.—This fluid, which is discharged from the urethra, consists of spermatozoa derived from the testes, together with the secretions of the accessory sexual glands. It is a sticky yellowish-white fluid, containing an odorous body named spermatin. Its reaction is neutral or just alkaline. When exposed to the air after some of the watery portion has evaporated, rhomboidal crystals appear. These are identical with Charcot-Leyden crystals, and are said to be derived from the prostatic fluid.

Spermatozoa.—A spermatozoon is a minute filiform body about 50 μ in length. It consists of a head which is chiefly nucleus; this is surmounted by a head cap with a sharpened extremity, a short neck which contains two centrosomes, a middle portion or body which is traversed by an axial filament, and a long cilium-like projection or tail which is also traversed by an axial filament. The head varies greatly in size and in shape in different animals, being characteristic for each species. The spermatozoon of man has a flattened oval-shaped head, appearing somewhat pointed when seen in profile, with a depression on each flattened surface. The head is composed chiefly of chromatin, and stains deeply with basic dyes. The middle portion or body is nearly cylindrical, being 6 μ in length and 1 μ in diameter. It has a spiral fibre passing round it. In the spermatozoon of man no very definite structure can be seen, although in some animals the structure appears very definite. The tail is much finer than the body, and terminates in a still finer end piece.

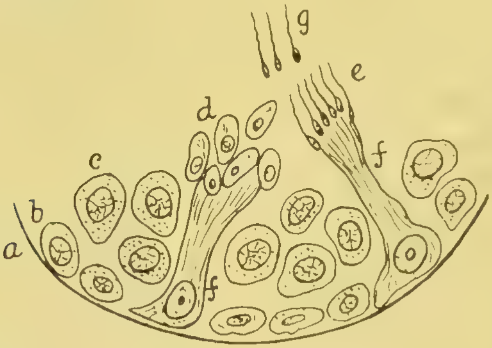


FIG. 135.—Diagram to represent the phases of spermatogenesis.

a = Basement membrane of seminiferous tubule.
b = Spermatogonia lying upon the basement membrane.
c = Spermatocytes with large nuclei.
d = A clump of spermatoblasts or spermatids connected to the free portion of a cell of Sertoli, *f*, which is supported upon the basement membrane.
e = Spermatozoa clinging to a cell of Sertoli *f*.
g = Free spermatozoa in the lumen of the seminiferous tubule.

After the spermatozoa are shed they exhibit spontaneous movements for many hours; this is due to the vibratory or ciliary movements of the tail.

SPERMATOGENESIS.—The spermatozoa are developed from the epithelium which lines the walls of the seminal tubules. The cells which constitute this epithelium are of three kinds, differing in situation, in size, and in structure (*vide* Fig. 135).

(1) *Spermatogonia* form the outermost zone. They are cubical cells forming a regular single layer next to the basement membrane of the seminal tubule. These are the only variety of cells found in the seminal tubules of the fœtus.

By karyokinetic division they give rise to the cells of the next zone. Between the spermatogonia some of the cubical cells which line the seminal tubules become elongated; these elongated cells are the cells of Sertoli (nurse cells). The free end of these cells becomes connected with groups of the newly developed spermatozoa.

(2) *Spermatocytes* form the intermediate layer. They are large cells, each containing a very well defined nucleus which exhibits karyokinesis. They form a layer two or three cells deep, and give rise to the cells of the next layer.

(3) *Spermatoblasts* or *spermatids* are small granular cells, each with a round nucleus. They are derived from the spermatocytes, and are directly transformed into spermatozoa. Each group of newly formed spermatozoa becomes connected with a supporting cell of Sertoli, which most probably nourishes the spermatozoa. In developing into spermatozoa the spermatoblasts become elongated, the nucleus alters in shape and passes towards one end of the cell, where it forms the main portion of the head of the spermatozoon. A filament forms within the protoplasm, and grows outwards to form the tail. The protoplasm of the cell partly remains to form the body or middle portion, and partly becomes disintegrated and detached as the maturation of the spermatozoon is completed. It has been found that when, in the cock, the testes are transplanted into the peritoneal cavity they continue to produce spermatozoa; hence spermatogenesis is independent of nervous influences. Sexual maturity and the development of secondary sexual characters in the male are, in all probability, due to the presence of an internal secretion produced by the interstitial cells of the testes (*vide* p. 292).

Sexual maturity is reached at puberty, which in man appears to be about the age of fifteen years. At this period the testes enlarge and begin to produce spermatozoa. At the same time the secondary sexual characters usually make their appearance. The bones and muscles increase in size, there is a growth of hair upon the face and pubes, and an increase in size of the larynx, which causes the voice to become stronger and deeper. The general character and appearance of the individual become masculine.

When, however, the testes are removed by castration prior to the onset of puberty these changes do not occur; this shows that they are dependent upon the integrity of the testes.

2. **The Accessory Sexual Glands.**—These include the vesiculæ seminales, the prostate gland, and the glands of Cowper. That these glands play an essential part in the sex functions is shown by the fact that they atrophy in animals which undergo castration. They do not develop if this operation is performed before puberty.

The fecundity of animals (*e.g.* white rats) is much reduced if the vesiculæ seminales are removed, and procreative power is entirely lost if the prostate gland is also removed.

Since it is possible to perform artificial insemination successfully with a mixture of spermatozoa from the epididymis and normal saline solution, the probable function of these accessory sexual glands is to secrete fluid which dilutes the secretion of the testes and so produces a watery substance, the seminal fluid, which is more suitable for ejaculation.

In rodents, and especially in guinea-pigs, the secretion of the vesiculæ seminales coagulates in the vagina and thus forms a plug which prevents the escape of spermatozoa. The coagulation is in all probability brought about by the presence of an enzyme in the prostatic secretion.

THE VESICULÆ SEMINALES.—These are two flattened sacculated bodies situated at the base of the bladder, between it and the rectum. Each joins with the vas deferens at its termination to form the common ejaculatory duct.

Each vesicula seminalis is a membranous sac having a thin muscular coat and a mucous membrane. The muscular coat consists of two layers, an outer longitudinal and an inner circular. The mucous membrane is traversed by fine rugæ forming an alveolar structure somewhat like that present in the gall-bladder. The superficial epithelium is columnar, with a deeper layer of small polyhedral cells.

THE PROSTATE GLAND.—This gland consists of three lobes, the two lateral lobes being united both in front and behind the urethra by a middle lobe. Externally the prostate is invested by a dense fibrous capsule which is continuous with a recto-vesical fascia.

The parenchyma of the prostate consists of two chief portions—

(1) Plain muscular tissue, which forms the bulk of the stroma.

(2) Glandular structure, consisting of numerous tubular acini, which unite into a smaller number of excretory ducts. The acini are lined by columnar epithelial cells, and there is usually present a second layer of small cells next to the basement membrane. Corpora amylacea, rounded homogeneous bodies, are often present embedded in the epithelium of the acini.

Prostatic fluid is a thin milky fluid having a seminal odour. In reaction it is slightly acid, occasionally it is amphoteric.

COWPER'S GLANDS.—These are two small racemose glands situated between the two layers of the triangular ligament, the ducts of which open near the anterior end of the bulbous portion of the urethra. Each gland consists of several small lobules held together by a firm capsule containing plain muscle. The acini of the glands are lined by columnar epithelial cells, those lining the duct are flattened columnar.

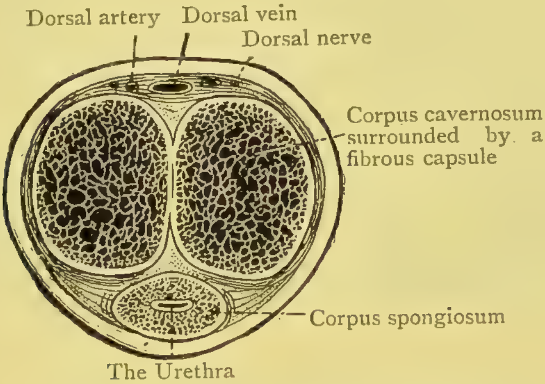


FIG. 136.—Transverse section through the body of the penis. (Cunningham.)

3. **The Penis.**—This is the intromittent organ by means of which the seminal fluid is introduced within the female. The penis consists of erectile tissue arranged in three cylindrical masses, the two dorsal corpora cavernosa, and the ventral median corpus spongiosum (*vide* Fig. 136). Each of these is surrounded by a strong fibrous tunica albuginea. The corpus spongiosum is channelled by the urethra, and anteriorly it is somewhat expanded to form the glans penis, which is invested by the prepuce.

The glands of Tyson, the glandulæ odoriferæ, are modified sebaceous glands situated around the corona glandis. Their secretion possesses a peculiar odour.

THE MECHANISM OF ERECTION.—The erectile tissue of the penis consists of numerous interlacing trabeculæ of fibrous tissue and plain muscle, enclosing a series of intercommunicating venous spaces or sinuses lined by endothelial cells and containing blood. Erection is due to the filling of the sinuses of the erectile tissue with arterial blood, whereby the organ becomes larger, more rigid, and redder. The helicine arteries become uncoiled, the arterioles dilate, and so fill the erectile tissue with blood. The outgoing venous trunks are compressed through the contraction of the muscles at the root of the penis. The arterioles are innervated by the nervi erigentes, or the pelvic splanchnic nerves. In the dog these arise from the second, third, and fourth sacral nerves, and contain *vaso-dilator* fibres. The centre for erection of the penis, which is present in the lumbar region of the spinal cord, may be excited reflexly by afferent impulses starting in the sensory nerves of the penis, and by psychical impulses from the brain. Coitus is essentially a reflex act, in all probability innervated through a centre in the lumbar region of the cord. Although it is usually attended with complex and characteristic psychical changes, it can be carried out in animals even when the spinal cord is completely transected in the lower dorsal region.

CHAPTER LVI.

THE FEMALE REPRODUCTIVE ORGANS AND FŒTAL MEMBRANES.

THE FEMALE REPRODUCTIVE ORGANS.

The reproductive organs of the female consist of—

1. The ovaries, which produce the ova.
2. The Fallopian tubes, along which the ova pass to
3. The uterus, in which the fœtus is developed.
4. The vagina and the external genitals.

1. **The Ovaries.**—These consist of a pair of flattened oval glandular bodies, each of which lies in the fossa ovarica, near the side wall of the pelvis, and is connected with the back of the broad ligament of the uterus.

Each ovary consists of a fibrous tissue stroma or framework containing blood vessels, nerves, lymphatics, and plain muscle fibres, with an outer covering of columnar epithelium, the remains of the primitive germ epithelium. Embedded in the stroma are the Graafian follicles containing ova. Near the hilum of the ovary are polyhedral cells, of a yellowish colour, closely resembling the interstitial cells of the testis; they are the interstitial cells of the ovary, and in all probability produce the internal secretion of the ovary (*vide* p. 292). The outer layer of the ovarian stroma is somewhat condensed, and free from Graafian follicles; it constitutes the tunica albuginea.

Structure of a Graafian Follicle. — Immature Graafian follicles lie in the cortical layer of the ovary beneath the tunica albuginea. They consist of a single layer of spindle-shaped cells like those of the ovarian stroma from which they are derived; these closely invest the contained ovum. The number of immature Graafian follicles in the ovaries of the new-born child has been estimated at 70,000, of which the greater number obviously never reach maturity.

The maturing follicles, fewer in number, are somewhat larger, and lie deeper in the stroma of the ovary, whilst still larger and more mature follicles advance from the deeper ovarian tissue and arrive near the surface of the ovary.

A mature Graafian follicle consists of—

1. The *tunica fibrosa.*—This outer tissue is condensed ovarian stroma.

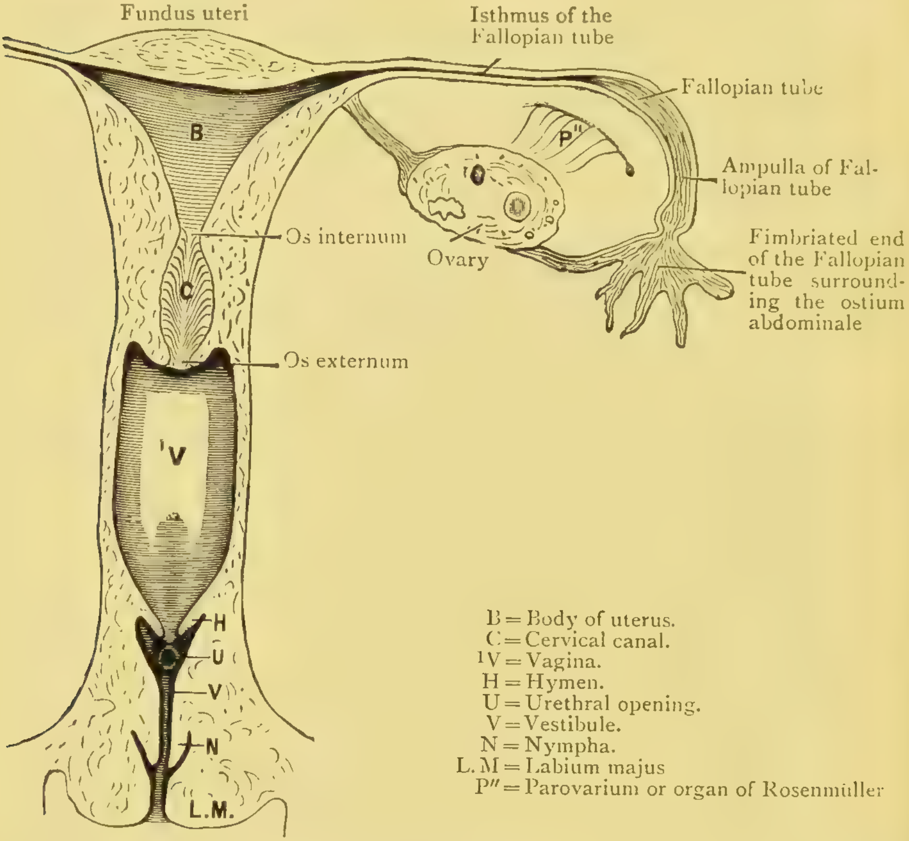


FIG. 137.—Diagram of the vulva, vagina, and the uterus, with its appendages. (Cunningham, *after* Symington.)

2. The *membrana propria* or basement membrane.

3. The *membrana granulosa*, a layer of nucleated columnar epithelial cells lining the inner aspect of the membrana propria.

4. The *discus proligerus, or cumulus* —This is a heaping up of the cells of the membrana granulosa at one part of the follicle, so as to enclose the ovum.

5. The *ovum.*
6. The *liquor folliculi*, the fluid of the follicle.

The mature Graafian follicle projects from the surface of the ovary, and then ruptures, shedding its contents—the ovum and the liquor folliculi—into the peritoneal cavity close to the abdominal ostium of the Fallopian tube. The rupture of the follicle takes place through the thin avascular projecting portion of the ovarian wall known as the stigma. The giving way of the stigma constitutes the dehiscence of the follicle, and the shedding of the ovum is known as *ovulation.* Each Graafian follicle usually contains a single ovum, but it may be binovular or even tri-ovular.

After a mature Graafian follicle has ruptured, the cells lining its wall multiply and hypertrophy, forming masses of large yellow cells. Between these cells are trabeculæ of vascular tissue derived from the surrounding ovarian stroma. These little bodies are the *corpora lutea.* If pregnancy supervenes, the corpus luteum becomes larger and persists longer than in the unimpregnated condition. At the end of pregnancy in the human being the corpus luteum is about half an inch in diameter.

The Structure of the Ovum.—On its discharge from the Graafian follicle, the human ovum is a spherical vesicle just visible as a clear speck to the naked eye, being about 0·2 mm. in diameter. It consists of the following parts :—

1. An external envelope known as the *zona pellucida*, zona radiata, or the striated membrane of the ovum. The striæ in this membrane are minute pores for the passage of nutrient material; they also in all probability allow of the passage of the spermatozoon into the ovum.

A micropyle has been described as present in the zona radiata of the ova of some mammals.

2. The *vitellus*, or yolk, contained within the zona radiata. It is a semifluid substance consisting of protoplasm with a fine reticular structure which contains the yolk granules, fat granules, pigment, and other granules of a high refractive index, constituting the deutoplasm.

3. The *germinal vesicle*, which constitutes the nucleus of the ovum. It is large, spherical, and often eccentric. It possesses a nuclear membrane which encloses the intranuclear network, within the meshwork of which is the clear nuclear sap.

4. The *germinal spot*, or macula germinativa, is the round nucleolus within the germinal vesicle.

OÖGENESIS.—The ova and the cells present in the Graafian follicles are derived from the germ epithelium on the surface of the ovary. From these cells rounded elongated masses of cells which constitute the egg-tubes of Pflüger grow down into the ovarian stroma. These cells are the oögonia; some of the oögonia enlarge to form ova or oöcytes, the others form the epithelial cells of the follicles.

2. **The Fallopian Tubes.**—These tubes constitute the oviducts, since they convey the ova from the ovaries into the cavity of the uterus. The Fallopian tubes are enclosed in the free margins of the broad ligaments, and measure 4 or 5 inches in length.

Each tube is divided into—

1. THE ISTHMUS.—This constitutes the inner third of the tube, and opens by a small orifice into the uterine cavity.

2. THE AMPULLA.—This extends from the isthmus to the neck of the tube. It constitutes rather more than half the length of the tube.

3. THE NECK, WITH ITS ORIFICE, known as the ostium abdominale.

4. THE INFUNDIBULUM, PAVILION, OR THE FIMBRIATED EXTREMITY.—This is the trumpet-shaped ovarian end of the tube, fringed by a number of irregular processes called the fimbriæ, one of which, being attached to the ovary, constitutes the ovarian fimbria.

Structurally the Fallopian tube consists of four coats—

1. The peritoneal coat externally.

2. A muscular coat of plain muscle fibres arranged in two layers, an external longitudinal and an inner circular layer; these layers are not readily differentiated from one another.

3. A submucous coat.

4. A mucous membrane lined by a columnar ciliated epithelium. The mucous membrane is thrown into longitudinal plicæ, which gradually increase in size and in complexity from the uterine to the ovarian end of the tube.

3. **The Human Uterus.**—This is a hollow muscular organ, pyriform in shape, somewhat flattened from before backwards, with its lower end projecting into the vagina. It measures 1 inch in thickness, 2 inches in breadth at its upper or widest part, and 3 inches in length, having walls half an inch

thick. The uterine cavity is 2½ inches in length. The uterus is divided into three parts—the fundus, the body, and the neck.

The *fundus* is the convex upper part of the body which projects above the attachments of the Fallopian tubes.

The *body* gradually narrows from the fundus to the neck. The anterior surface of the body is flat, and its posterior surface convex. The body measures 2 inches in length.

The *neck*, or cervix uteri, is continuous above with the body; it is the lower free end of the uterus, and projects into the vagina. The cervix is somewhat conical in shape, and measures about one inch in length; it is divided into three parts: the supravaginal, the intermediate, and the infravaginal portion, according to their relations to the attachments of the vaginal walls. The lower end of the cervix, which projects into the vagina, is known as the vaginal portion, or portio vaginalis. It opens into the vagina by a rounded or transverse aperture, the external os uteri. The cavity of the uterus is triangular in shape, and flattened from before backwards, so that its anterior and posterior walls are in apposition. The three angles correspond with the openings of the Fallopian tubes above and the internal os uteri below. The internal os is situated at the junction of the body and cervix, where the cavity is somewhat constricted. The spindle-shaped cavity of the cervix extends from the os internum to the os externum. The inner surface of the walls of the cervix are rugose, the rugæ forming the arbor vitæ, which is more strongly marked on the anterior than on the posterior wall.

THE STRUCTURE OF THE UTERUS.—1. *The external serous covering, or peritoneal layer.*—The peritoneum covers the fundus of the uterus on its anterior surface as far down as the level of the internal os, where it is reflected forwards on to the bladder. It also covers the whole of the posterior surface extending downwards to the pouch of Douglas.

2. *The muscular coat* constitutes the major portion of the bulk of the uterus, and is composed of interlacing bundles of plain muscle fibres of small size. Except for a thin superficial sheet immediately beneath the peritoneum, the muscular coat of the uterus is considered to be an immensely hypertrophied muscularis mucosæ, as is shown by the arrangement and the ramification of the blood vessels in the uterine wall.

The mucous membrane of the uterus consists of the uterine glands embedded in a stroma, and is lined by a single layer of columnar ciliated epithelial cells. The glands are simple tubes, consisting of a basement membrane upon which is a layer of columnar cells continuous with those of the body of the uterus. The stroma of the mucous membrane consists of a fine reticulum of connective-tissue fibres, in which there are numerous small round and spindle-shaped cells embedded. The cervix uteri is lined by a firmer and more fibrous mucous membrane similar in structure to that of the body, except that the epithelium is composed of shorter cells and that the glands penetrate more deeply into the underlying muscular layer. Externally the cervix is lined by a stratified epithelium which is continuous with that of the vagina.

MENSTRUATION.—The endometrium of the non-pregnant uterus undergoes a cycle of changes, which result in the periodic discharge of blood, known as menstruation.

The menstrual cycle is divided into four stages :—

1. The Stage of Quiescence.
2. The Constructive Stage.
3. The Destructive Stage.
4. The Stage of Repair.

The Stage of Quiescence.—This has been already described as the normal condition of the uterus.

The Constructive Stage.—This stage commences as soon as the process of repair (following the preceding menstrual period) is completed, *i.e.* about eighteen days after the cessation of the previous menstrual flow. The mucous membrane becomes considerably increased in thickness, partly by cell division, partly by an increase in the intercellular stroma, and partly by an enlargement of the utricular glands and blood vessels, an enlargement which results in the production of a sero-sanguinous exudate which infiltrates the stroma.

The Destructive Stage.—In this stage blood leaves the capillaries and becomes extravasated freely in the stroma, partly by diapedesis of the corpuscles, and partly by rupture of capillaries. The blood tends to accumulate in the lacunæ, which lie beneath the superficial epithelium. These lacunæ constitute the so-called sub-epithelial hæmatomata. The epithelium becomes lifted off its bed, and the resulting space between it and the stroma becomes filled with blood.

The rupture of these sub-epithelial hæmatomata allows of the escape of the blood into the lumen of the uterus, and into the lumina of the glands.

The escaping blood, in normal circumstances, does not clot; menstrual blood appears to be devoid of fibrin enzyme.

The Stage of Repair.—As soon as the flow has ceased regenerative changes begin to appear in the endometrium. The extravasated blood is gradually absorbed, the dilated vessels shrink, and such cells as are lost become replaced by the multiplication of those which remain.

Of the twenty-eight days of the normal menstrual cycle, about five are occupied by the premenstrual congestion, four by the menstrual flow, seven by the period of repair, and twelve by the quiescent stage.

4. **The Vagina.**—This is a dilatable musculo-membranous passage extending from the vulva to the uterus, its upper part being expanded to receive the vaginal portion of the cervix uteri. Its anterior wall is about 2½ inches long, its posterior wall being 3½ inches long.

The vagina is lined by a stratified epithelium. Its anterior and posterior walls show a slightly elevated longitudinal ridge extending mesially upwards; these ridges are the columns of the vagina. At right angles to these columns are transverse ridges in the mucous membrane; these are the rugæ of the vagina.

The External Genitals.—These are known as the vulva or pudendum. They comprise the mons veneris, the labia majora and minora, the clitoris and the hymen, along with the glands of Bartholin, which are the homologues of Cowper's glands in the male.

COPULATION AND FERTILISATION.

As the result of coitus ejaculation occurs, and spermatozoa are deposited in the vault of the vagina. By their own movements, aided possibly by the suction action of the uterus, the spermatozoa traverse the uterine cavity to reach a Fallopian tube, in the outer end of which they meet the ovum which has been shed by the bursting of a Graafian follicle.

The ovum falls into the abdominal ostium of the tube, and becomes propelled along the tube by the activity of its cilia, which work towards the uterus.

At the outer end of the Fallopian tube spermatozoon and ovum meet, unite, and fertilisation occurs.

The tail of the spermatozoon appears to become absorbed, the head remains as the *male pronucleus.* After the nucleus of the ovum has extended its two polar bodies, and in this way has got rid of half of its original number of chromosomes (*maturation*), it becomes the *female pronucleus.* The male pronucleus, which contains the same number of chromosomes as the female pronucleus, and the female pronucleus unite to form the segmentation nucleus (*fertilisation*), which now contains the normal number of chromosomes characteristic of the species.

The ovum is also entered by the middle piece of the spermatozoon, which then induces the formation of a centrosome, which, after the completion of fertilisation, initiates the process of cell division. Cytoplasmic filaments become arranged in a star-like manner around the centrosome, forming the sperm-aster. The fertilised ovum, also called the oösperm or zygote, is thus produced, and forms the starting-point of that series of cell divisions which eventually result in the formation of a newly developed individual.

SEGMENTATION.

After fertilisation has become completed the oösperm undergoes cleavage, or segmentation, dividing first into two, and each of these again dividing into two, and so on, until there is formed a more or less globular mass of cells, or blastomeres. This mass of cells is the mulberry mass or morula. This process of segmentation of the ovum has never been observed in the human ovum, but it has been studied in the ova of the rabbit, in which the fertilised ovum divides into two; there is complete division of the cell, and the segmentation is therefore of the holoblastic type. There is, however, no reason to suppose that the segmentation of the human ovum materially differs from that of other mammals.

In the morula a cavity soon appears, and the mass then forms a blastula, or blastocyst.

The blastula is at first unilaminar except at one pole, where an inner group of irregular cells collects to form an inner cell mass. This inner cell mass soon grows, and gradually extends round the cavity, the wall of which then becomes bilaminar. The outer of the two layers constitutes the *epiblast*, and the inner the *hypoblast*.

This bilaminar blastoderm is called the gastrula; its cavity communicates with the exterior by a small aperture, the blastopore. Later, a third layer of cells appears between these two, the blastoderm becomes trilaminar, and the new intermediate layer constitutes the mesoblast.

The organs of the developing embryo are developed from the three layers of the blastoderm as follows:

From the Epiblast.

(*a*) The epidermis of the skin and its appendages.

(*b*) The epithelial structures of the sense organs, *i.e.* the crystalline lens.

(*c*) The epithelium of the mouth and the enamel of the teeth.

(*d*) The epithelium of the nasal passages.

(*e*) The epithelium of the glands opening on to the skin and into the mouth and nasal passages; the anterior lobe of the pituitary body.

(*f*) The muscular fibres of the sweat glands.

(*g*) The central and peripheral nervous system; the posterior lobe of the pituitary body and the pineal gland.

From the Mesoblast.

(*a*) The skeleton and all the connective tissues of the body, including the dermis.

(*b*) All the muscles of the body (except those of the sweat glands).

(*c*) The vascular system, including the lymphatics, and the lymphatic glands, the spleen, and the serous membranes.

(*d*) The urinary and the reproductive organs, except the epithelium of the bladder, and that of the urethra, which is hypoblastic.

From the Hypoblast.

(*a*) The epithelium of the alimentary canal, and that of all the glands (including the liver and the pancreas) opening into it.

(*b*) The epithelium of the respiratory tract.

(*c*) The epithelium of the Eustachian tube and the tympanum.

(*d*) The epithelium lining the vesicles of the thyroid gland.

(*e*) The epithelial nests (corpuscles of Hassall) of the thymus gland.

(*f*) The epithelium of the bladder and of the urethra.

To follow out the development of the organs of the body in detail constitutes the science of Embryology, and will not be dealt with here.

FŒTAL MEMBRANES AND PLACENTA.

The implantation of the fertilised ovum within the uterus, and the structures which are immediately concerned with the nutrition of the developing embryo, must now be considered.

The ovum, fertilised in the outer portion of the Fallopian tube, is propelled by the action of the cilia into the uterine cavity, and settles down upon its mucous membrane, in which it embeds itself by the phagocytic action of its outer layer, called the **trophoblast.**

In the unimpregnated state the mucous membrane of the uterus is known as the endometrium. As soon as fertilisation is accomplished, the uterine mucous membrane undergoes certain changes, and then becomes known as the decidua.

The differences between the decidua and the normal endometrium may be summed up as follows:

1. The formation of decidual cells.
2. The hypertrophy and dilatation of the deepest parts of the utricular glands.
3. An increased vascularity leading to the formation of widely dilated capillaries or sinuses, together with interstitial hæmorrhages.
4. Extensive loss of the epithelium from the surface.
5. A division of the lining into two layers, the superficial or compact, and the deep, spongy, or cavernous layer.
6. A great increase in thickness, the decidua being one-eighth to three-quarters of an inch in thickness, and the endometrium one-twenty-fifth to one-sixth of an inch in thickness.

Three portions of the decidua are differentiated:—

1. The *decidua basalis* or *serotina.*—This is the portion which is in contact with the base of the ovum.
2. The *decidua capsularis* or *reflexa.*—This portion encloses the remainder of the ovum.

3. The *decidua vera.*—This portion lines the remainder of the uterine cavity, and does not come into direct contact with the ovum.

Between the decidua vera and the decidua capsularis is the decidual space, *i.e.* the remains of the uterine cavity. As the developing embryo enlarges, these two membranes come into contact, and eventually fuse, thus obliterating the decidual space. In the human subject this occurs in the early part of the fourth month of gestation.

In the nutrition of the early embryo, due to the activity of the trophoblast, the nutrient material appears to be transmitted from cell to cell; later this path becomes inadequate, and the nutrition of the embryo is then obtained from the yolk sac, or umbilical vesicle and the allantois. The former is of relatively little importance, and the umbilical vesicle soon atrophies, and the allantoic circulation is soon replaced by the placental circulation which is developed in the chorion. The chorion is one of the two special fœtal envelopes, the chorion and amnion, which serve for the nutrition and the protection of the fœtus. These membranes appear to be formed much earlier in the human subject than they do in the chick, from which the description of their development is usually taken. In the chick they are formed by the formation and subsequent fusion of the head and tail folds of the fœtal membranes.

The chorion forms the outer layer called the trophoblast, and is composed of two layers of cells, an outer layer consisting of a multinucleated mass of protoplasm, undivided into cells, and known as the *syncytium*, and an inner layer of cubical cells forming Langhans' layer.

In the first six weeks of development, the chorion is universally covered with complex branching vascular villi. Later these villi atrophy over the whole surface of the embryo, except where it is attached to the decidua basalis, and form a smooth membrane known as the *chorion læve.* Where the ovum is attached to the decidua basalis, the villi hypertrophy, and become united by intergrowth with the decidua basalis which also becomes hypertrophied. This portion of the chorion constitutes the *chorion frondosum*, and the fused chorion frondosum and decidua basalis eventually form *the placenta.*

The amnion lines the chorion internally, and encloses the amniotic sac, which contains the developing fœtus and also a certain amount of fluid known as the liquor amnii, which serves to protect the fœtus from external violence, from undue pressure, and from changes of temperature.

The Liquor Amnii.—At the end of a full term of pregnancy the quantity of liquor amnii present varies from 10 to 50 oz. It is a clear liquid of specific gravity 1002 to 1010, is slightly alkaline in reaction, and contains a little protein, and a small amount of urea, sodium chloride, and ammonium carbonate, also epithelial cells from the skin and bladder of the fœtus.

The Placenta.—It has been already stated that the placenta is formed by the fusion and intergrowth of the decidua basalis, which forms the maternal portion of the placenta, and the chorion frondosum, which forms the fœtal part of the placenta. As a separate organ, the placenta dates from the third month of pregnancy, and from that time gradually increases in size until the termination of pregnancy. The chorionic villi lose Langhans' layer of cells, and embed themselves into the interglandular stroma of the decidua basalis, and sometimes penetrate the mouths of the small veins. The syncytium also penetrates the endothelium of the decidual arterioles, and large blood sinuses are thus formed. By this arrangement, the fœtal and maternal blood, while kept separate, are brought into such close contact that osmosis may readily occur between them, thus permitting the absorption of nutritive material from the maternal into the fœtal circulation, the excretion of urea and other waste products of fœtal metabolism, the passage of oxygen to the fœtus, and the excretion of carbon dioxide from it.

The functions of the placenta may be summed up as follows:

1. It is nutritive, allowing of the passage of nutritive material to the fœtus.

2. It is respiratory. Oxygen passes to, and carbon dioxide from, the fœtus.

3. It is excretory, allowing the escape of urea and other products of fœtal metabolism.

4. It has a glycogenic function. Glycogen is stored in its cells for the future use of the fœtus.

5. It is iron storing, by which iron in organic combination is passed from the maternal circulation into the fœtal circula-

tion to be stored in the liver cells of the fœtus, in order to aid in the formation of new coloured blood corpuscles.

At full term the placenta is a discoidal mass about 7 inches in diameter, two-thirds of an inch in thickness, and weighs about 16 oz. Its fœtal surface is smooth and covered by the amnion, and its maternal surface is divided by sulci into a number of irregular areas termed cotyledons. The fœtus is attached to it by the umbilical cord or funis, which averages 20 inches in length and half an inch in thickness. It consists of a stroma of Wharton's jelly, embedding the two umbilical arteries and a single umbilical vein. It is covered by the amnion.

PARTURITION.

When pregnancy has lasted 280 days, uterine contractions known as labour pains set in, and parturition occurs, *i.e.* the contents of the pregnant uterus are expelled.

Parturition is usually divided into three stages.

In the *first stage of labour* those contractions of the uterus, which normally occur at intervals during the course of a pregnancy without any apparent effect upon the uterine contents, become distinctly augmented. They occur rhythmically, and involve a gradual contraction succeeded by an equal gradual relaxation. As labour progresses their intensity and frequency increase. These movements result in the dilatation of the os uteri, and in the coercion of the fœtal membranes, with contained liquor amnii, into the external os. The rupture of the fœtal membranes usually occurs at the end of this stage.

During the course of *the second stage* the head of the fœtus is pressed into the os uteri. Then the movements of the uterus become more prolonged and more frequent, and movements of the abdominal muscles, voluntary and reflex, also occur. The abdominal muscles are associated, in their contraction, with fixation of the diaphragm, so that the pressure in the abdominal cavity is greatly increased. In this way the fœtus is expelled through the vagina, and finally emerges from the vulva head first.

The *third stage* comprises the expulsion of the after-birth. About from twenty to thirty minutes after the birth of the child, the movements of the uterus are renewed, and the placenta and fœtal membranes are expelled.

The movements of parturition are controlled by a centre situated in the lumbar cord, entirely independent of cortical control. This is shown by some observations of Goltz. This observer transected the cord of a bitch in the dorsal region. Subsequent to the transection, it exhibited the phenomena of heat (menstruation). It was impregnated, and a normal pregnancy and parturition followed. More recently still, Goltz and Ewald have demonstrated that even the presence of the nerve centre is not necessary, for in a dog with complete removal of the cord below the lower dorsal region, parturition succeeded a normal pregnancy. The sensory nerves involved in the reflex, if any, remain undiscovered. The motor nerves concerned are the third, fourth, and the fifth lumbar nerves which supply autonomic fibres via the hypogastric nerves. It is well known that emotions, *e.g.* anger, rage, are able to exert an effect upon the centre.

The reason for parturition is not known, though many hypotheses have been advanced, such as the distension of the uterus, pressure of the fœtus, the accumulation of carbon dioxide in the blood, degenerative changes in the placenta, and the presence of hormones in the maternal blood, produced either by the fœtus or the placenta.

After parturition is completed the puerperium ensues. During this period the reproductive organs gradually return to the condition in which they were before pregnancy occurred. The breasts become active, so as to perform the function of lactation (*vide* p. 77).

The changes which occur in the uterus are known as *involution*, and during the process of involution, which occupies six to eight weeks, the uterus gradually diminishes in size. This change appears to be due to the activity of autolytic enzymes, and not, as is usually alleged, to fatty degeneration of the uterine wall.

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